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Synthesis of Alkynyl-substituted Camphor Derivatives and their Use in the Preparation of Paclitaxel-related Compounds.

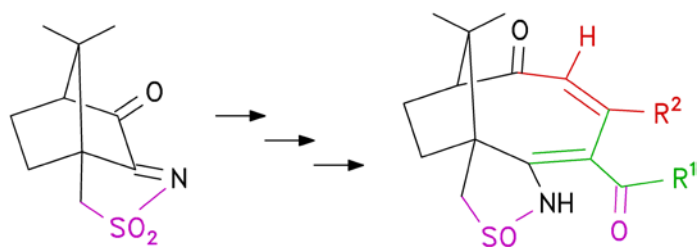
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Graphical Abstract



3-Oxo-camphorsulfonylimine was converted into alkyne-substituted camphor derivatives. The 2,3-bis-alkynyl derivatives undergo a platinum-catalysed cycloisomerisation to provide compounds whose carbon skeleton resembles paclitaxel to some extent.

Abstract

Compounds containing two alkyne groups in close vicinity at the rigid skeleton of camphorsulfonamide show unique reactivities when treated with electrophiles or catalytic amounts of platinum(II), the product structures depending not only on the reagents but also on the substituents attached to the triple bonds. Cycloisomerisations with perfect atom economy lead to polycyclic heterocycles that resemble to some extent the AB ring system of paclitaxel. Herein, we present practical synthetic methods for the selective synthesis of precursor dialkynes bearing different substituents (alkyl, aryl) at the triple bonds, based on ketals or an imine as protecting groups. We show for isomeric dialkynes that the reaction cascade induced by Pt(II) includes ring annulation, sulfur reduction and ring enlargement. One isomeric dialkyne additionally allows for the isolation of a pentacyclic compound lacking the ring enlargement step, which we have proposed as a potential intermediate in the catalytic cycle.

Keywords

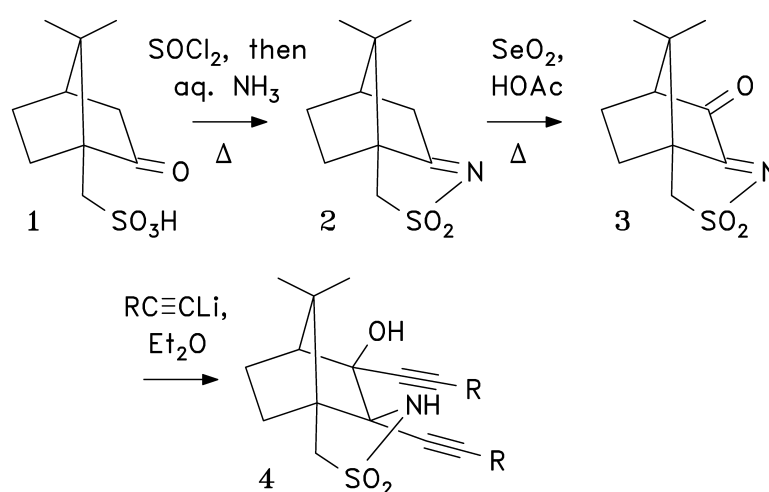
Camphor derivatives, alkynes, platinum, catalysis, cycloisomerisation

Introduction

Enantiomerically pure raw materials, available in a sustainable manner from the natural “chiral pool” [1], offer a convenient entrance for the chemical synthesis of other chiral compounds, e.g. rare natural products and their analogues [2], or chiral catalysts [3,4]. A prominent example for such a “chiral pool” starting material is camphor. Both its substituents and its bicyclic skeleton can easily be modified and adapted to the purpose at hand, e.g. natural product synthesis [5]. Wagner-Meerwein and Nametkin-type rearrangements are the most common reaction patterns [6], and the addition of organometallic reagents to the camphor carbonyl group allows for selective introduction of additional substituents and functional groups (e.g. as in [7]). Camphor was the source of chirality in

Holton's taxol synthesis [8] and other approaches to the taxane group of compounds [9-11].

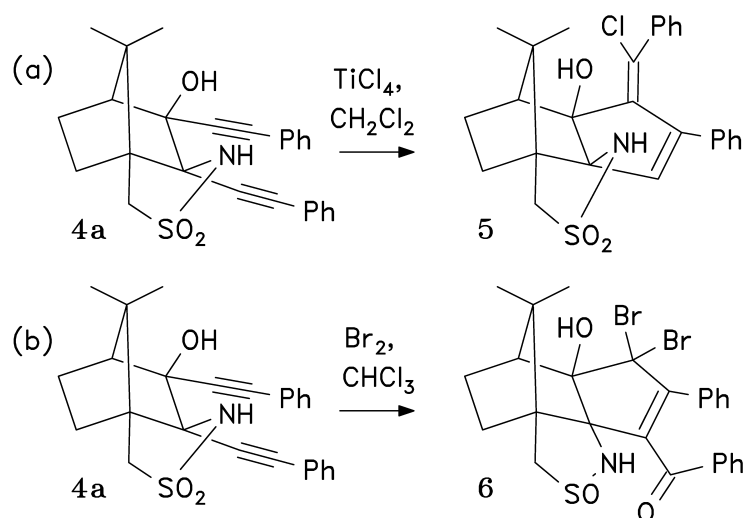
From cheap camphor-10-sulfonic acid (**1**), a cyclic sulfonimide **2** can easily be obtained which is readily converted into useful auxiliaries [12], or oxidized to the oxoimide **3** (Scheme 1) [13-15]. This versatile intermediate can be reduced to provide a chelating ligand for chiral catalysis [16], or oxidized to oxaziridines used as efficient chiral oxidizing reagents [13,17-19].



Scheme 1. Synthesis of 3-oxo-camphorsulfonylimine (**3**) [13,15] and its bis-alkynyl derivatives **4** from camphor-10-sulfonic acid (**1**).

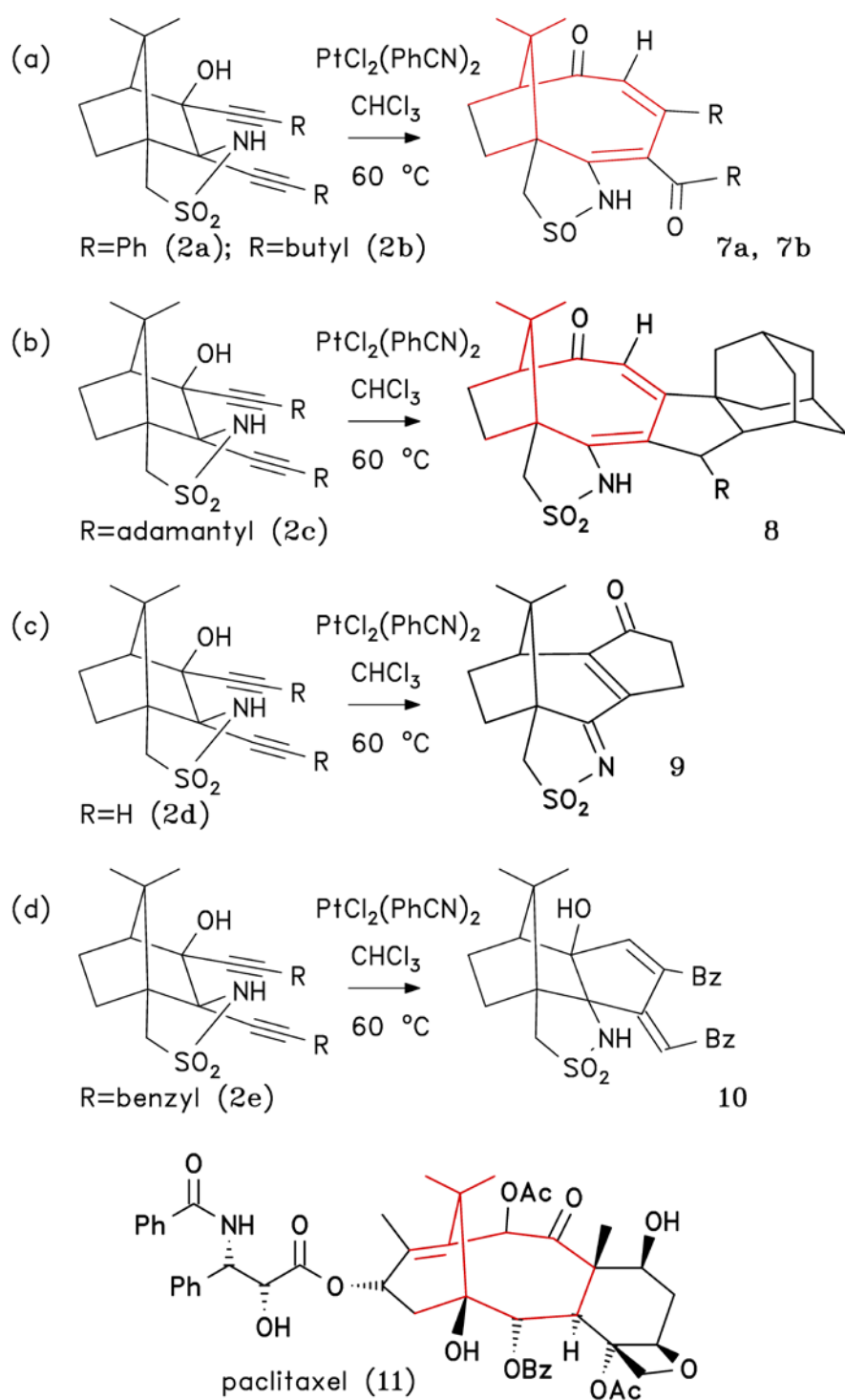
Reaction of the oxoimide **3** with two equivalents of the lithium salt of a terminal alkyne leads to compounds **4** where two alkynyl substituents, a sulfonamide and a hydroxy group are found in vicinal positions (Scheme 1) [20]. A hydroxy group neighbouring an alkynyl substituent, under treatment with acids, normally leads to Rupe and Meyer-Schuster rearrangements, forming unsaturated carbonyl compounds. This was indeed observed in camphor-derived bicyclic alcohols containing a single ethynyl group [21,22], occasionally accompanied by Wagner-Meerwein rearrangement [23], but no such products were found with any of the diynes **4**. Our first attempts to employ **4a** as a ligand with Ti(IV) resulted, somewhat surprisingly, in addition of HCl under simultaneous annulation (three carbon expansion [24,25]) of a carbocyclic five-membered ring to the 2,3-position of the bicyclic

camphor-derived moiety (Scheme 2a) [20]. Reactions of **4a** with halogens (e.g. bromine) or acids were even more puzzling. In addition to the annulation, an unprecedented formation of a ketone accompanied by reduction of sulfur took place, to give a cyclic sulfinamide **6** (Scheme 2b) [26]. In this case, the mechanism of the reaction via cationic intermediates could be established by in situ NMR spectroscopy.



Scheme 2. Reactions of bis-alkynyl camphor derivative **4a** with TiCl_4 , and with Br_2 .

Catalysis by Pt(II) can drive the reaction even further: besides annulation and sulfur reduction, one finds a cleavage of the C-C bond between the atoms bearing the OH and NH groups (ring enlargement). The result is an isomerisation of **4a** and **4b** to form tricyclic compounds **7** containing a nine-membered carbocyclic ring (Scheme 3a) [27]. Isomerisations are the best examples for a perfect “atom economy” [28-30] since all atoms of the starting material are found in the product, and thus fulfill an important requirement of “green chemistry” [31].



Scheme 3. Reactions of bis-alkynyl camphor derivatives **4** with catalytic amounts of $\text{PtCl}_2(\text{PhCN})_2$.

A different Pt(II)-catalysed reaction cascade was observed for **4c**, with adamantyl groups at the alkynes. Here, the annulation step is followed by a C-H bond activation process, to establish an additional bond to one of the adamantyl groups (**8** in Scheme 3b) [32]. The simplest diyne **4d** with R=H, in contrast, gave a ring enlargement from six to seven members together with a 1,2-oxygen shift instead (**9** in Scheme 3c) [33]. This clearly demonstrates that the substituents at the triple bonds have a decisive influence on the outcome of the catalytic reaction. This was also confirmed by the reaction of **4e** (R = benzyl): in addition to the expected product **7** in analogy to that of **4b**, there was also a considerable amount of a reduced species **10** lacking sulfur reduction and ring enlargement, with structural similarity to the simple product from the Ti(IV) reaction with **4a**. The reducing agent is Pt(II) which is oxidised to Pt(III) during the reaction (Scheme 3d) [34].

Scheme 3 also depicts paclitaxel (**11**), an important anti-cancer drug, as there are some similarities (shown in red in Scheme 3) but also differences to our compounds obtained by Pt(II) catalysis from e.g. **4a**. The eye-catching dimethylmethylene bridge over the largest carbocyclic ring is of course the most striking similarity, although this ring is in our compounds one carbon unit smaller (9 vs. 10 members in taxol) and lacks the oxygen substituent bearing the amino acid side group. In both compounds, we find a keto group in the largest ring. Instead of the six-membered ring annulation in taxol, there are the substituents of the original triple bonds in our compounds, precisely in the same positions. And where taxol has the bridgehead hydroxy and its neighbouring benzoate groups, we find the heterocyclic reduced isothiazole ring in the product of the Pt(II) catalysis. Other camphor derivatives prepared as entrance to taxoid compounds have a carbocyclic ring at this place in the precursor [10] and a nine-membered ring with a keto group after oxidative bond cleavage [11]. The similarities between our materials and taxol do, of course, not mean that similar biological activity is necessarily involved, but it might be worthwhile investigating.

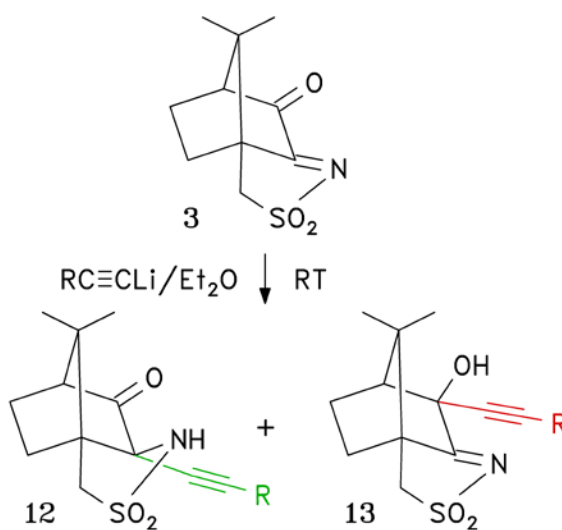
Since the results of the Pt(II) catalysis depend on the nature of the substituents at the alkyne groups, it would be of interest to explore the course of the reaction when the two

substituents are different. In this article, we develop reasonable synthetic procedures for the starting diynes, and present the first result of a catalytic Pt(II) reaction of such mixed substituted compounds.

Results and Discussion

For the preparation of the diynes **4**, a 2:1 ratio (or slightly larger for complete reaction) of the lithium salt of a terminal alkyne and of the oxoimide **3** is applied. The ratio should, however, not be increased too much. For instance, with benzylacetylene, the expected diyne **4e** (Scheme 3d) is obtained, with only traces of monosubstituted compounds. However, with a 3:1 ratio, the main product is formed by reaction of only one equivalent of lithium salt with the C=N double bond, leaving the carbonyl group intact. In addition, the new propargyl group is isomerized to an allene moiety, obviously by the excess of the strongly basic lithium salt [35]. This unexpected monosubstitution remains unexplained and cannot be used as basis for a general selective synthesis of monoalkynyl camphor derivatives. Alkynes can also be cleaved from the bis-alkynyl compounds **4** by reaction with CuCl, but again, there are selectivity issues that prevent a general application [36]. We therefore set out to explore whether some selectivity is observed when lithium salts of terminal alkynes are reacted with the oxoimide **3** in a 1:1 ratio (Table 1). As alkyne precursors, phenylacetylene, 1-heptyne, 1-ethynyladamantane and 1-ethynyl-1-methoxycyclohexane were used. In all cases, mixtures of **12** and **13**, together with starting oxoimide **3** and the bis-alkynyl product **4** were obtained. Very slow addition of the acetylide and dilute oxoimide solutions slightly improved the yields of the mono-adducts **12** and **13**, but the formation of the bis-adducts could not be fully suppressed. With increasing bulk of the alkyne substituent (R = adamantyl, methoxycyclohexyl) the reaction tends to become more selective towards mono-addition, but less selective with respect to the alkylation site, and the 2-alkynyl and 3-alkynyl products are formed in similar amounts. Alkynes with small substituents (e.g. heptyne or phenylacetylene) preferentially attack at the C=N bond of the sulfonylimine, suggesting that the carbon atom of the C=N

is more electrophilic than that of the C=O bond. With bulkier alkynes (e.g. 1-adamantylacetylene or 1-methoxy-1-ethynyl-cyclohexane), attack at the carbonyl group becomes more pronounced. Presumably, the C=O carbon atom in 3-oxo-camphorsulfonylimine is sterically more accessible, whereas the sulfonylimine C=N carbon is more electrophilic. Steric and electronic properties thus counteract and the overall selectivity of the reaction depends on a balance between both factors.



Entry	R	12 : 13	Yield 12+13
a	Phenyl	80:20	42 %
b	n-pentyl	90:10	35 %
c	1-adamantyl	70:30	88 %
d	1-methoxycyclohexyl	50:50	67 %

Table 1. Selectivity in the reaction of oxoimide **3** with alkynyl lithium compounds.

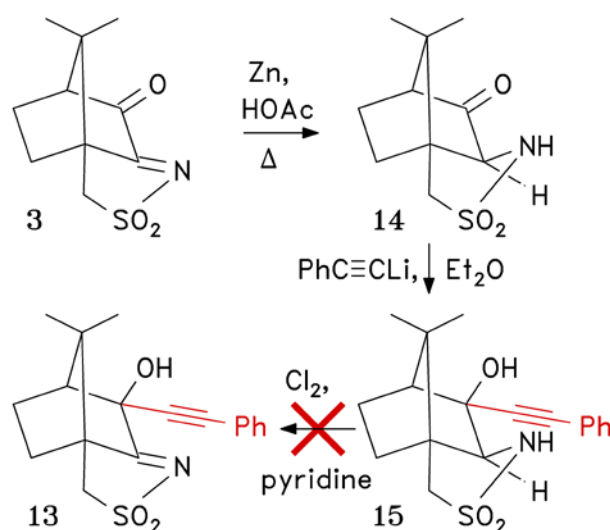
Whilst chromatographic separation of the mixture of the monoadducts **12** + **13** from the starting material **3** and the bis-adduct **4** is straightforward, the isolation of pure **12** and **13** requires careful control of the chromatography conditions (SiO₂, CHCl₃/diethyl ether gradient 0 to 10 %), and has been used on a small scale for analytical purposes only. The

ratios **12** : **13** given in Table 1 were determined by integration of the signals of the methyl groups in the ^1H NMR, and ratios in the crude product and after isolation of the mixture of **12** and **13** by chromatography were found consistent.

In the IR spectra, compounds **12** show a typical NH stretching vibration at approximately 3217 cm^{-1} , and a C=O stretch at 1764 cm^{-1} . Compounds **13**, in contrast, can be recognised by their OH stretching vibration at 3444 cm^{-1} and the C=N stretch at 1653 cm^{-1} . Both compounds display a C \equiv C stretch at very similar wavenumbers around 2227 cm^{-1} , and asymmetric and symmetric SO₂ stretching vibrations. These are found at about 1314 and 1143 cm^{-1} in compounds **12**, and at slightly higher wavenumbers of approx. 1330 and 1160 cm^{-1} in **13**. In the ^1H NMR spectra, the signals of the geminal methyl groups come with a chemical shift difference of about 0.2 ppm in **12**, but almost coincide to form one signal in compounds **13**. The opposite holds true for the diastereotopic protons of the CH₂SO₂ moiety, which nearly coincide in **12**, but come as two doublets spaced about 0.2 ppm apart in **13**. Compounds **12** display a singlet near 5 ppm for the SO₂NH proton, whereas **13** show a singlet for the OH group at about 3.2 ppm . Similarly, the ^{13}C NMR signals of the methyl groups nearly coincide in **13** but are approximately 2 ppm apart in **12**. Compounds **12** show a signal for the C=O near 206 ppm and one for the sulfonamide carbon at about 65 ppm . In compounds **13**, there is a signal for the C=N around 194 ppm and one for the tertiary alcohol carbon near 73 ppm . All other signals of the camphor framework and the alkynyl substituent come at relatively similar values and do not allow to distinguish between **12** and **13** reliably.

In view of the above results, it was clear that a more selective method was needed that generally allows for mono-alkynylation and for differentiation between the carbonyl group and the sulfonylimine. One way to achieve this could be in the chemoselective reduction of either the C=N group of oxoimide **3**, addition of the alkynyl moiety to the carbonyl group, and re-oxidation of the sultam to the sulfonimide (see Scheme 4). A number of reductions of oxoimide **3** have been described in the literature, using a variety of reducing agents. All

of them lead either to complete reduction or unselective reduction of the C=N and C=O bond. Thus, LiAlH_4 reduces the C=O and C=N group of **3**, and 3-exo-hydroxy-camphorsultam is obtained in good yields [16]. Under Meerwein-Ponndorf-Verley conditions ($\text{Al}(\text{O}^i\text{Pr})_3/i\text{PrOH}$) a mixture of the 3-hydroxy-imine, 3-oxo-camphorsultam and 3-exo-hydroxy-camphorsultam is produced. Prolonged reaction over several weeks eventually leads to 3-exo-hydroxy-camphorsultam as the sole product.

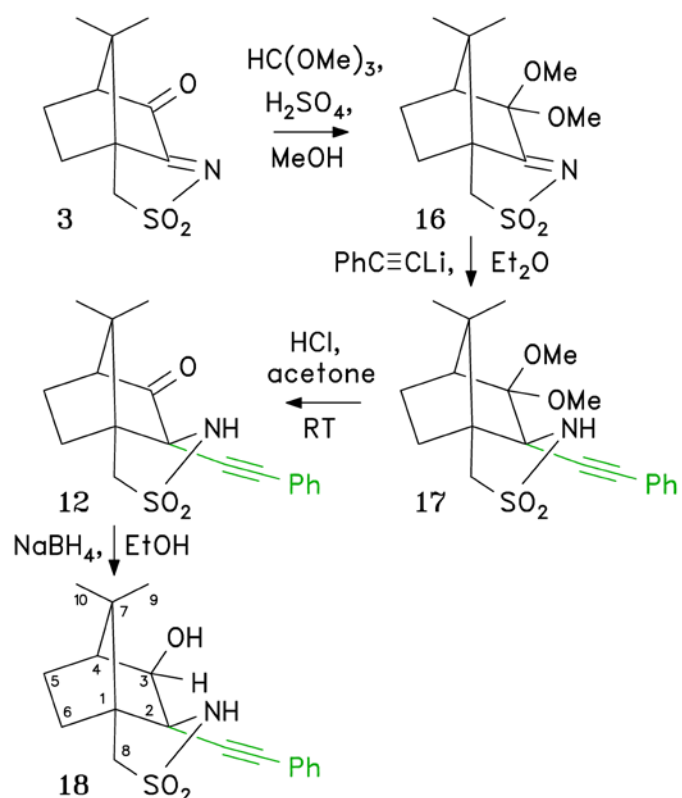


Scheme 4. Attempted selective synthesis of 3-alkynyl derivatives via sulfonylimine reduction of oxoimide **3**.

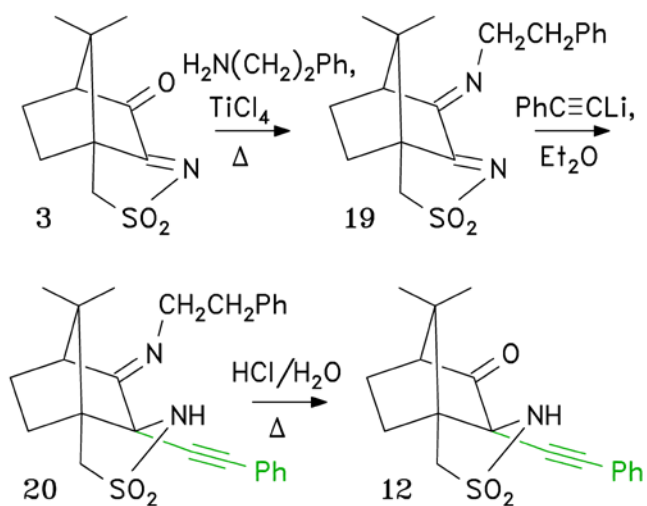
We now found that the sulfonylimine of **3** can be reduced selectively to the sultam **14** in the presence of Zn/HOAc , as shown in Scheme 4. The product shows an IR stretching vibration at 1760 cm^{-1} and a ^{13}C NMR signal at 209.7 ppm for the unreacted C=O group. The presence of the sultam can be deduced from the NH stretching vibration at 3180 cm^{-1} , a ^{13}C signal of the sulfonamide carbon at 65.0 ppm and a ^1H NMR signal for the NH at 5.57 ppm . These data are very similar to those of compound **12** where C=O and sulfonamide coexist. In contrast to **12**, the ^1H NMR signal of the NH in **14** comes as a doublet, due to coupling with the adjacent CH proton at 3.58 ppm , which is also split into a doublet. Introduction of an alkynyl substituent into the 3-position does not pose any problem and can be achieved by reaction with $\text{PhC}\equiv\text{CLi}$ under standard conditions, to

produce **15** in high yields. Two equivalents of the acetylide are needed because the first one deprotonates the nitrogen of the sultam before the second equivalent undergoes the desired nucleophilic addition to the carbonyl group. Attempts to re-oxidise the sultam **15** to the sulfonimide **13**, using $\text{Cl}_2/\text{pyridine}$ [37] or $\text{N-tert-butylphenylsulfonimidoyl chloride/DBU}$ [38] under literature conditions, were unsuccessful due to the sensitivity of the alkyne to oxidising conditions.

Our next strategy was to modify the carbonyl group in the 3-position and introduce the alkyne at the sulfonamide side, as shown in Schemes 5 and 6. The carbonyl group in **3** can be protected selectively as an acetal by reaction with orthoformates at room temperature in the presence of an acid. Thus, 3,3-dimethoxy-camphersulfonylimine (**16**) and 3,3-diethoxy-camphersulfonylimine (**16'**) were prepared [18,39]. Subsequent reaction of these acetals with one equivalent of lithium phenylacetylide or 1-heptynyl lithium under conditions described above for the synthesis of **12** and **13** introduced the alkyne into the 2-position of the camphor skeleton, to provide the sultams **17**. Removal of the acetal protecting group occurred under comparatively mild conditions by stirring a mixture of **17** with acetone and conc. HCl . Acetone as solvent was best as it allows for trans-acetalisation to acetone dimethylacetal and **12** rather than hydrolysis to methanol and **12**. Overall, yields are higher throughout when the methyl acetal is used. To obtain the camphor-derived hydroxysultam **18** bearing an alkyne substituent in 2-position rather than in 3-position, **12** was reduced with NaBH_4 under standard conditions. Compound **18** was made for comparison of the analytical data with that of compound **15**. Although the IR spectra look fairly similar, the two isomers can be distinguished from their NMR spectra, in particular ^1H and ^{13}C signals of the atoms in 2 and 3 position. Thus, the proton in the 3-position in **18** comes at higher chemical shift than the one in the 2-position in **15** (4.31 ppm vs. 3.67 ppm). Likewise, the signals of carbons 2 and 3 are further downfield, when a hydrogen is attached to them. Also carbon 4 is affected and appears at higher chemical shift in **15** where the alkynyl substituent is nearby.



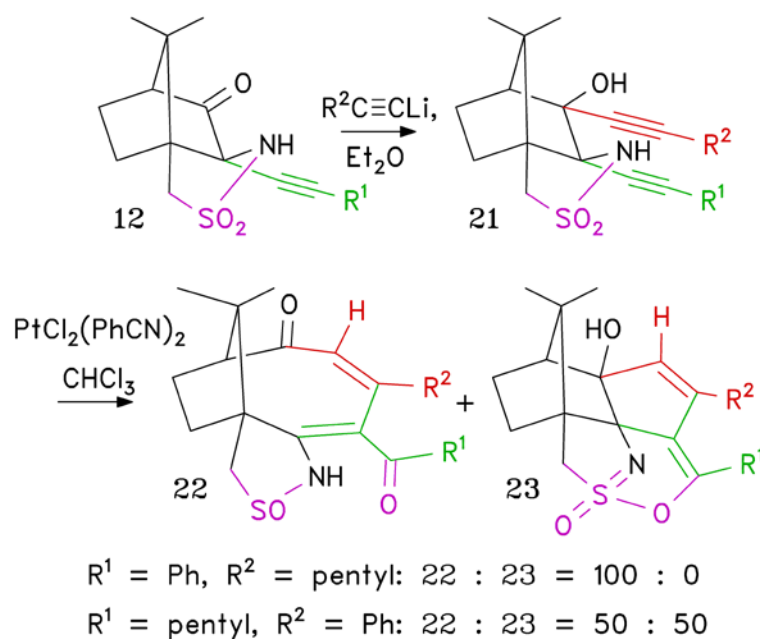
Scheme 5. Selective synthesis of 2-alkynyl derivatives by protection of the 3-oxo group as an acetal.



Scheme 6. Selective synthesis of 2-alkynyl derivatives by protection of the 3-oxo group as an imine.

As an alternative to the introduction of an acetal, an imine was tested for its suitability as a protecting group for the carbonyl moiety, as shown in Scheme 6. 3-Oxo-camphorsulfonylimine (**3**) was converted into the imine **19** by reaction with 2-phenylethylamine in the presence of TiCl_4 [40]. Reaction of **19** with one equivalent of the lithium phenylacetylide under the conditions described above for the synthesis of **12** and **13** provided the sultam **20** selectively, with exclusive introduction of the alkyne into the 2-position at the camphor skeleton [41]. When two equivalents of the acetylide are used, the reaction still produces **20** only, and no reaction at the 3-position in the imine was observed. The high selectivity of this reaction can be explained by the large difference between the electron deficient sulfonylimine and the electron rich imine. The sulfonylimine carbon atom is significantly more electrophilic and thus more prone to attack by the acetylide. In the case of 3-oxo-camphorsulfonylimine, this difference between the reactive functional groups ($\text{C}=\text{O}$ vs. $\text{C}=\text{N}-\text{SO}_2\text{R}$) was much less pronounced, leading to poor selectivity. The general ^1H and ^{13}C signal pattern of the camphor skeleton in compound **20** is fairly similar to the one found for compounds **12**, indicating that the alkyne has indeed been introduced at the sulfonamide side. Also the ^{13}C signal at 175.8 ppm shows clearly the presence of the imino group in 3-position. For a sulfonimide, a signal at higher ppm values (approx. 190 ppm) would have been expected. The removal of the imine protecting group turned out to be somewhat difficult and could only be performed under relatively harsh acidic conditions with aqueous HCl under reflux to provide **12** in moderate yield. Overall, protection of the carbonyl group as an acetal appears more convenient than as an imine.

Starting from the 2-alkynyl-3-oxo compound **12a**, the mixed bis-alkynyl compound **21a** was prepared by reaction with 1-heptynyl lithium, and accordingly, **21b** was obtained from reaction of **12b** with $\text{PhC}\equiv\text{CLi}$ (Scheme 7) [41,42]. Two equivalents of the alkynyl lithium compound are necessary because the first one is used for deprotonation of the relatively acidic proton at the sulfonamide nitrogen.



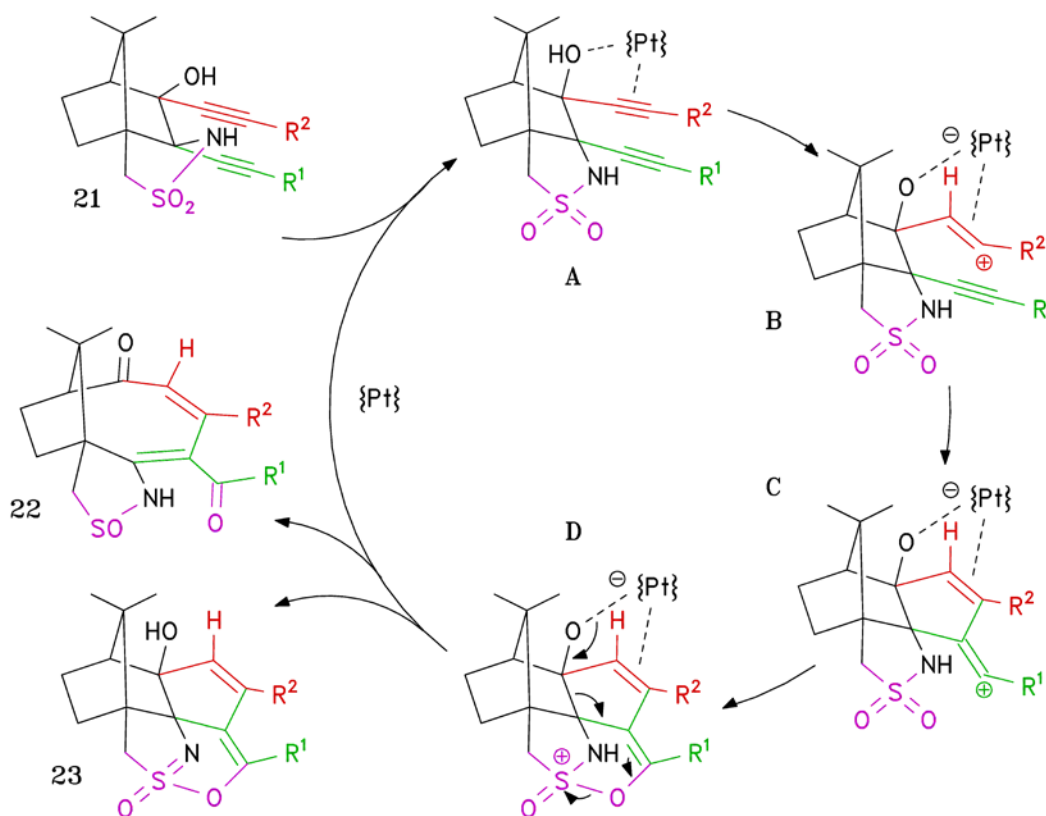
Scheme 7. Synthesis of the bis-alkynyl derivatives bearing different alkyne substituents and their platinum catalysed cycloisomerisation. Compounds **21a** and **22a**: $R^1 = \text{Ph}$, $R^2 = \text{pentyl}$; compounds **21b**, **22b** and **23**: $R^1 = \text{pentyl}$, $R^2 = \text{Ph}$.

Compounds **21a** and **21b** were then reacted with 5 mol % $\text{PtCl}_2(\text{PhCN})_2$ at 60 °C in CHCl_3 [42]. For ^1H NMR monitoring, the same conditions were applied, but CDCl_3 was used as solvent. Within 10 hours, compound **21a** converts cleanly into product **22a**, and no intermediates or side products were detected. Under microwave irradiation, the reaction can be completed within 30 min at 80 °C, without impairing the selectivity. The structure of **22a** is analogous to the one observed previously with the bis-phenylalkynyl compound [27] as a starting material. Cyclisation of the alkynes and a three carbon ring enlargement lead in a single step to a rare bicyclic carbon framework that bears some similarity to that of the anti-cancer drug paclitaxel. Remarkably, the sulfonamide group was reduced to a sulfinamide in the course of the reaction, and one of the former alkynyl carbons was oxidised to a ketone. The presence of the sulfinamide can be deduced from the fragmentation pattern in the mass spectrum where the loss of SO can be seen, and also from the IR spectrum. Only one S=O vibration can be identified at 1098 cm^{-1} , in a similar position as the S=O vibrations in DMSO (1050 cm^{-1}) or t-butylsulfinamide (1032 cm^{-1})

[43]. The strong band at about 1330 cm^{-1} , typical for the asymmetric S=O stretch in sulfonamides and sulfones, is absent in **22a**. The IR spectrum also shows the presence of two carbonyl groups at 1680 and 1611 cm^{-1} , and these are confirmed in the ^{13}C NMR spectrum (signals at 198.3 and 210.8 ppm). The NH of the sulfinamide seem to be strongly involved in hydrogen bonding with the carbonyl group nearby, as evidenced from the NH stretching vibration in the IR at 3110 cm^{-1} and the ^1H NMR signal at an unusually high chemical shift of 11.97 ppm . The ring expanded carbon skeleton has been corroborated from $^1\text{H}/^{13}\text{C}$ NMR together with 2D experiments, which allowed for a complete and unequivocal assignment of all signals.

Upon reaction with catalytic amounts of $\text{PtCl}_2(\text{PhCN})_2$, compound **21b** converts into two products, apparently in a parallel reaction, and these were separated by chromatography. One product is the expected **22b**, whose structure is analogous to **22a** described above. The other one, **23**, has undergone alkyne cyclisation but the ring expansion has not yet taken place. The sulfonamide reduction and formation of the ketone are just about to occur, as the oxygen atom involved is on its way of being transferred from the sulfur onto the carbon atom. The structure of **23** was established by two-dimensional $^1\text{H}/^{13}\text{C}$ NMR experiments, and by comparison with relatively similar compounds obtained in the reaction of the bis(phenylalkynyl)-derivative of **4a** with triflic acid [26], or with $\text{K}[\text{ReO}_4]$ [27]. The polycyclic carbon skeleton in these is identical, but the latter compounds are protonated at the sulfonimide nitrogen and form the triflate or perrhenate salts. The newly formed five-membered ring in **23** is evident from the ^{13}C NMR signals at 84.0 , 90.0 , 138.5 , 136.0 and 125.5 ppm , and a ^1H signal at 5.80 ppm . The enolate carbon is detected at 151.4 ppm in ^{13}C NMR. Neither NMR nor IR shows any evidence for carbonyl groups, but there is a medium intense C=C stretching vibration at 1653 cm^{-1} and two strong bands at 1324 cm^{-1} and 1059 cm^{-1} for the asymmetric and symmetric stretches of the O=S=N moiety. Compared to the SO_2 moiety in sulfonamides (e.g. **21b** with 1330 cm^{-1} and 1128 cm^{-1}) the symmetric stretch is at unusually low wavenumbers.

The formation of products **22** and **23** can be explained from the proposed reaction mechanism, shown in Scheme 8. Attack of the catalyst at the OH and possibly at the alkyne in the immediate neighbourhood could be inferred from the fact that the ^1H signal of the OH of **21** broadens significantly upon addition of $\text{PtCl}_2(\text{PhCN})_2$. Concomitantly, a small amount of uncoordinated PhCN is observed in the ^1H NMR spectrum. The coordinated Pt center, as a Lewis acid, promotes the release of the OH proton from **A** and its transfer onto one of the alkyne carbons to form intermediate **B**. The resulting vinylic carbocation undergoes an electrophilic attack at the neighbouring alkyne, which in turn reacts with the sulfonamide oxygen nearby. Both steps are strongly facilitated by the geometry changes when the linear alkyne moieties convert into bent alkene ones, as the reactive center is literally pushed into the functional group it next reacts with. Intermediate **D** can be seen as the common precursor for the parallel formation of the observed products, **23** by dissociation from the Pt catalyst and proton migration from the sulfonamide to the alcoholate, and **22** by a cascade of electron movements as indicated by the arrows in **D**.



Scheme 8. Proposed mechanism of the platinum catalysed cycloisomerisation.

Conclusion

Several methods for the synthesis of camphor-derived dialkynes having two different alkynyl substituents in close vicinity to each other and to a sulfonamide group were developed. Ketals turned out to be most efficient for the protection of carbonyl groups, leading to pure dialkynes with a well defined substitution pattern. The reactivity of a pair of isomers containing a phenyl and a pentyl group attached to the triple bonds towards cycloisomerisation induced by Pt(II) catalysis was studied. The expected annulation – sulfur reduction – ring enlargement cascade leading to a product resembling paclitaxel to some extent was found in both cases. However, one of the isomers yielded a second product lacking the ring enlargement step and containing an additional sulfur – oxygen – carbon linkage. The platinum complex of this compound was postulated before as an intermediate in the sulfur reduction step of the cascade reaction, and the isolated product thus supports our mechanistic considerations. Platinum(II) catalysis applied to camphor-derived dialkynes with two different substituents can thus not only give valuable insight in the mechanism of such cycloisomerisations and help to clarify the role of the substituents, but also yield a novel type of taxoid compounds of complex polycyclic structures with potential biological effects.

Supporting Information File 1: Experimental Section containing a description of the materials and instrumentation, and the preparation of the new compounds, as well as the ^1H and ^{13}C NMR spectra of compounds **12a**, **12b**, **13a**, **17a**, **17b**, **18**, **19**, **20**, **21a**, **21b**, **22a**, **22b** and **23**.

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Supporting Information

Synthesis of Alkynyl-substituted Camphor Derivatives and their Use in the Preparation of Paclitaxel-related Compounds.

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Experimental Section

Materials and Instrumentation. 3-Oxo-camphorsulfonylimine (**3**) [13,15] and the 3,3-dialkoxy-camphorsulfonylimines **16** and **16'** [18] were prepared according to the literature. Reactions involving carbanions or TiCl_4 were carried out in an N_2 -atmosphere. Syntheses under microwave irradiation were performed in an Anton Paar Monowave 400 reactor in sealed vials. C, H, N and S elemental analyses were carried out on VarioEL III CHNS and Leeman CE-440 CHN elemental analyser. Melting points were determined with a Büchi 530 apparatus in open capillaries. For TLC, Merck UV 254 SiO_2 -plates have been used. Mass spectra were obtained on a Thermoquest MAT 95XL instrument. Infrared spectra ($4000\text{--}400\text{ cm}^{-1}$) were recorded on Perkin Elmer 2000 FTIR and Nicolet Avatar 320 FT-IR instruments in KBr pellets. ^1H and ^{13}C one- and two-dimensional NMR experiments were performed on Varian UNITY 300, Varian MERCURYplus 400, Bruker AM 360, Bruker AV 500 and Bruker DRX 500 spectrometers at ambient temperature. Signals were assigned with the help of COSY, NOESY, HMQC, HSQC and HMBC spectra.

Preparation of the Mono-alkyne derivatives **12** and **13** from 3-oxo-camphorsulfonylimine (**3**).

Similar as described in [33], a solution of the alkyne (2.1 mmol) in dry diethyl ether (5 ml) was cooled in an ice bath. Butyl lithium (1.6M in hexanes, 1.25 ml, 2 mmol) was added and the reaction mixture was left at room temperature for 30 min, before it was added dropwise to a suspension of 3-oxo-camphorsulfonylimine (**3**) (460 mg, 2 mmol) in dry diethyl ether (5 ml). The reaction mixture was stirred overnight, water (5 ml) was added and the organic phase was separated. The aqueous phase was extracted twice with dichloromethane, and the combined organic phases were dried with Na_2SO_4 . After chromatography on SiO_2 (eluent $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ 9:1) the mixture of the 2- and 3-substituted compounds **12** and **13** was obtained as a colourless oil (**12** and **13** elute together). From

this mixture, the ratio **12:13** was determined by ^1H NMR spectroscopy. Compounds **12** and **13** could be separated by chromatography on SiO_2 , using a CHCl_3 /diethylether gradient 0 to 10 % as eluent.

a) Reaction with phenylacetylene:

Yield is 42 %, **12a:13a** = 80:20. Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_3\text{S}$: C, 65.65; H, 5.81; N, 4.25; S, 9.71. Found: C, 65.40; H, 5.80; N, 4.51; S, 9.68. CI-MS, m/z : (M is 329.421) 330 [$M + \text{H}$] $^+$.

(3aS,7aS)-8,8-Dimethyl-7-oxo-7a-phenylethynyl-1,4,5,6,7,7a-hexahydro-3H-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (12a).

Colourless solid. M.p. 147-148 °C. TLC on SiO_2 , R_f = 0.40 (eluent $\text{CHCl}_3/\text{Et}_2\text{O}$ 9:1). IR spectrum (selected bands), cm^{-1} : 3218 s $\nu(\text{NH})$, 2226 w $\nu(\text{C}\equiv\text{C})$, 1760 s $\nu(\text{C}=\text{O})$, 1312 and 1143 s $\nu(\text{SO}_2)$. ^1H NMR spectrum (500 MHz) in CDCl_3 , δ (ppm): 1.08 (s, 3H) and 1.26 (s, 3H)(H-9 and H-10), 1.89 (m, 1H), 2.08 (m, 2H) and 2.48 (m, 1H)(H-5 and H-6), 2.48 (m, 1H, H-4), 3.42 (d, J = 13.0 Hz, 1H) and 3.46 (d, J = 13.0 Hz, 1H)(H-8), 5.44 (s, 1H, NH), 7.30 (m, 3H) and 7.45 (m, 2H)(Ph). ^{13}C NMR spectrum (125 MHz) in CDCl_3 , δ (ppm): 19.9 and 22.8 (C-9 and C-10), 21.9 (C-5), 29.2 (C-6), 45.4 (C-7), 49.9 (C-8), 57.4 (C-1), 58.6 (C-4), 65.5 (C-2), 84.3 and 90.0 ($\text{C}\equiv\text{C}$), 121.6, 128.5, 129.4 and 132.2 (Ph), 205.7 (C-3).

(3aS,7R)-7-Hydroxy-8,8-dimethyl-7-phenylethynyl-4,5,6,7-tetrahydro-3H-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (13a).

Colourless solid. M.p. 160-162 °C. TLC on SiO_2 , R_f = 0.38 (eluent $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ 9:1). IR spectrum (selected bands), cm^{-1} : 3442 s $\nu(\text{OH})$, 2223 w $\nu(\text{C}\equiv\text{C})$, 1652 s $\nu(\text{C}=\text{N})$, 1334 and 1166 s $\nu(\text{SO}_2)$. ^1H NMR spectrum (500 MHz) in CDCl_3 , δ (ppm): 1.15 (s, 3H) and 1.16 (s, 3H)(H-9 and H-10), 1.90 (m, 1H), 2.09 (m, 2H) and 2.32 (m, 1H)(H-5 and H-6), 2.44 (d, J = 4.6 Hz, 1H, H-4), 3.20 (d, J = 13.2 Hz, 1H) and 3.33 (d, J = 13.2 Hz, 1H)(H-8), 3.41 (s, 1H, OH), 7.37 (m, 3H) and 7.50 (m, 2H)(Ph). ^{13}C NMR spectrum (125 MHz) in

CDCl₃, δ (ppm): 21.0 and 21.1 (C-9 and C-10), 23.9 (C-5), 27.8 (C-6), 47.5 (C-7), 50.1 (C-8), 56.0 (C-4), 64.2 (C-1), 73.4 (C-3), 85.5 and 89.0 (C \equiv C), 121.2, 128.4, 129.3 and 131.9 (Ph), 194.0 (C-2).

b) Reaction with 1-heptyne:

Yield is 35 %, **12b:13b** = 90:10. Anal. Calcd for C₁₇H₂₅NO₃S: C, 63.13; H, 7.79; N, 4.33, S, 9.91. Found: C, 62.99; H, 7.99; N, 4.14; S, 9.76. CI-MS, m/z : (M is 323.458) 324 [M + H]⁺, 260 [M - SO₂]⁺.

(3a*S*,7a*S*)-7a-Heptynyl-8,8-dimethyl-7-oxo-1,4,5,6,7,7a-hexahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (12b).

Colourless solid. TLC on SiO₂, R_f = 0.42 (eluent CH₂Cl₂/Et₂O 9:1). IR spectrum (selected bands), cm⁻¹: 3217 s v(NH), 2227 w v (C \equiv C), 1764 s v (C=O), 1314 and 1142 s v (SO₂). ¹H NMR spectrum (500 MHz) in CDCl₃, δ (ppm): 0.81 (t, 7.1 Hz, 3H, heptynyl-7), 1.02 (s, 3H, H-10), 1.21 (s, 3H, H-9), 1.29 (m, 4H, heptynyl-6 and -5), 1.45 (quint., J = 7.2 Hz, 2H, heptynyl-4), 1.75 (m, 1H, H-5 endo), 1.99 (m, 2H, H-6 and H-5 exo), 2.18 (t, J = 7.2 Hz, 2H, heptynyl-3), 2.39 (m, 1H, H-6), 2.38 (m, 1H, H-4), 3.32 ("s", 2H, H-8), 5.15 (s, br., 1H, NH). ¹³C NMR spectrum (125 MHz) in CDCl₃, δ (ppm): 14.2 (CH₃ heptynyl-7), 19.1 (CH₂ heptynyl-3), 20.0 (C-10), 21.9 (C-5), 22.3 (CH₂ heptynyl-6), 22.8 (C-9), 28.1 (CH₂ heptynyl-4), 29.2 (C-6), 31.2 (CH₂ heptynyl-5), 45.2 (C-7), 49.9 (C-8), 57.0 (C-1), 58.7 (C-4), 65.6 (C-2), 75.7 and 91.7 (C \equiv C), 206.3 (C-3).

(3a*S*,7*R*)-7-Heptynyl-7-hydroxy-8,8-dimethyl-4,5,6,7-tetrahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (13b).

Colourless solid. TLC on SiO₂, R_f = 0.40 (eluent CH₂Cl₂/Et₂O 9:1). IR spectrum (selected bands), cm⁻¹: 3452 s v(OH), 2227 w v (C \equiv C), 1653 s v (C=N), 1328 and 1155 s v (SO₂). ¹H NMR spectrum (400 MHz) in CDCl₃, δ (ppm): 0.82 (t, J = 7.2 Hz, 3H, heptynyl-7), 1.00 (s, 3H, H-10), 1.02 (s, 3H, H-9), 1.30 (m, 4H, heptynyl-6 and -5), 1.46 (m, 2H, heptynyl-4), 1.68 (m, 1H, H-5), 1.91 (m, 1H, H-6), 1.93 (m, 1H, H-5), 2.20 (t, J = 7.4 Hz,

2H, heptynyl-3), 2.04 (m, 1H, H-6), 2.15 (m, 1H, H-4), 3.08 (d, $J = 13.4$ Hz, 1H, H-8), 3.18 (d, $J = 13.4$ Hz, 1H, H-8), 3.20 (s, 1H, OH). ^{13}C NMR spectrum (100 MHz) in CDCl_3 , δ (ppm): 14.0 (CH_3 heptynyl-7), 19.0 (CH_2 heptynyl-3), 21.0 and 21.1 (C-9 and C-10), 22.2 (CH_2 heptynyl-6), 23.8 (C-5), 27.9 (C-6), 27.9 (CH_2 heptynyl-4), 31.2 (CH_2 heptynyl-5), 47.4 (C-7), 50.0 (C-8), 55.9 (C-4), 64.2 (C-1), 73.0 (C-3), 76.3 and 90.2 ($\text{C}\equiv\text{C}$), 194.4 (C-2).

c) Reaction with 1-adamantylacetylene:

Yield is 88 %, **12c:13c** = 70:30. Anal. Calcd for $\text{C}_{22}\text{H}_{29}\text{NO}_3\text{S}$: C, 68.18; H, 7.54; N, 3.61, S, 8.27. Found: C, 68.00; H, 7.89; N, 3.53; S, 8.11. EI-MS, m/z : (M is 387.545) 388 $[\text{M} + \text{H}]^+$, 324 $[\text{M} - \text{SO}_2]^+$, 135 [adamantyl] $^+$.

(3aS,7aS)-7a-(1-Adamantylethynyl)-8,8-dimethyl-7-oxo-1,4,5,6,7,7a-hexahydro-3H-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (12c).

Colourless solid. TLC on SiO_2 , $R_f = 0.48$ (eluent $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ 9:1). IR spectrum (selected bands), cm^{-1} : 3221 s $\nu(\text{NH})$, 2230 w $\nu(\text{C}\equiv\text{C})$, 1764 s $\nu(\text{C}=\text{O})$, 1316 and 1145 s $\nu(\text{SO}_2)$. ^1H NMR spectrum (400 MHz) in CDCl_3 , δ (ppm): 1.09 (s, 3H, H-10), 1.27 (s, 3H, H-9), 1.64 (m, br., 6H), 1.86 (m, br., 6H) and 2.00 (m, br., 3H)(adamantyl), 1.78 (m, 1H, H-5endo), 2.01 (m, 1H, H-6), 2.06 (m, 1H, H-5exo), 2.42 (m, 1H, H-6), 2.40 (d, $J = 5.0$ Hz, 1H, H-4), 3.37 ("s", 2H, H-8), 4.73 (s, br., 1H, NH). ^{13}C NMR spectrum (100 MHz) in CDCl_3 , δ (ppm): 19.8 (C-10), 21.8 (C-9), 22.7 (C-5), 27.7 (ada CH), 29.2 (C-6), 29.9 (ada C_q), 36.2 and 42.3 (ada CH_2), 45.0 (C-7), 49.6 (C-8), 56.7 (C-1), 58.5 (C-4), 64.9 (C-2), 74.4 and 99.0 ($\text{C}\equiv\text{C}$), 206.2 (C-3).

(3aS,7R)-7-(1-Adamantylethynyl)-7-hydroxy-8,8-dimethyl-4,5,6,7-tetrahydro-3H-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (13c).

Colourless solid. TLC on SiO_2 , $R_f = 0.45$ (eluent $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ 9:1). IR spectrum (selected bands), cm^{-1} : 3480 s $\nu(\text{OH})$, 2230 w $\nu(\text{C}\equiv\text{C})$, 1652 s $\nu(\text{C}=\text{N})$, 1326 and 1158 s $\nu(\text{SO}_2)$. ^1H NMR spectrum (400 MHz) in CDCl_3 , δ (ppm): 1.00 (s, 3H) and 1.09 (s, 3H)(H-9 and H-

10), 1.66 (m, 1H, H-6), 1.90 (m, 1H, H-5_{exo}), 1.93 (m, 1H, H-6), 2.03 (m, 1H, H-5_{endo}), 1.62 (m, br., 6H), 1.88 (m, br., 6H) and 2.01 (m, br., 3H)(adamantyl), 2.17 (d, J = 3.8 Hz, 1H, H-4), 3.13 (d, J = 13.4 Hz, 1H, H-8), 3.21 (d, J = 13.4 Hz, 1H, H-8), 3.18 (s, br., OH). ¹³C NMR spectrum (100 MHz) in CDCl₃, δ (ppm): 21.0 and 21.1 (C-9 and C-10), 24.0 (C-5), 27.6 (ada CH), 28.0 (C-6), 29.8 (ada C_q), 36.2 and 42.0 (ada CH₂), 47.4 (C-7), 50.1 (C-8), 55.9 (C-4), 64.2 (C-1), 73.0 (C-3), 76.1 and 98.3 (C≡C), 194.9 (C-2).

d) Reaction with 1-methoxy-1-ethynyl-cyclohexane:

Yield is 67 %, **12d:13d** = 50:50. Anal. Calcd for C₁₉H₂₇NO₄S: C, 62.44; H, 7.45; N, 3.83, S, 8.77. Found: C, 61.98; H, 7.52; N, 3.77; S, 8.89. EI-MS, *m/z*: (M is 365.495) 366 [M + H]⁺, 348 [M - H₂O]⁺, 334 [M - OMe]⁺, 270 [M - OMe - SO₂]⁺.

(3a*S*,7a*S*)-7a-(1-Methoxycyclohexyl)ethynyl-8,8-dimethyl-7-oxo-1,4,5,6,7,7a-hexahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (12d).

Colourless solid. TLC on SiO₂, R_f = 0.50 (eluent CH₂Cl₂/Et₂O 9:1). IR spectrum (selected bands), cm⁻¹: 3217 s ν(NH), 2228 w ν (C≡C), 1766 s ν(C=O), 1317 and 1143 s ν (SO₂). ¹H NMR spectrum (400 MHz) in CDCl₃, δ (ppm): 0.98 (s, 3H, H-10), 1.16 (s, 3H, H-9), 1.65 (m, 1H, H-5_{endo}), 1.93 (m, 1H, H-6), 1.97 (m, 1H, H-5_{exo}), 2.30 (m, 1H, H-6), 2.33 (d, J = 4.8 Hz, 1H, H-4), 3.22 (s, 3H, OMe), 3.26 ("s", 2H, H-8), 1.18 (m, 2H), 1.38 (m, 2H), 1.47 (m, 2H), 1.55 (m, 2H), 1.80 (m, 2H)(cyclohexyl), 5.01 (s, br., 1H, NH). ¹³C NMR spectrum (100 MHz) in CDCl₃, δ (ppm): 19.7 (C-10), 22.0 (C-5), 22.6 (C-9), 29.1 (C-6), 45.1 (C-7), 49.6 (C-8), 51.0 (OMe), 56.8 (C-1), 58.3 (C-4), 64.7 (C-2), 205.4 (C-3), 22.7, 25.3 and 36.4 (cyclohexyl CH₂), 74.2 (cyclohexyl C_q), 81.4 and 91.5 (C≡C).

(3a*S*,7*R*)-7-(1-Methoxycyclohexyl)ethynyl-8,8-dimethyl-7-hydroxy-4,5,6,7-tetrahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (13d).

Colourless solid. TLC on SiO₂, R_f = 0.48 (eluent CH₂Cl₂/Et₂O 9:1). IR spectrum (selected bands), cm⁻¹: 3444 s ν(OH), 2228 w ν (C≡C), 1655 s ν (C=N), 1322 and 1160 s ν (SO₂). ¹H NMR spectrum (400 MHz) in CDCl₃, δ (ppm): 0.99 (s, 3H) and 1.00 (s, 3H)(H-9 and

H-10), 1.68 (m, 1H, H-6), 1.90 (m, 1H, H-5 exo), 1.93 (m, 1H, H-6), 2.03 (m, 1H, H-5 endo), 2.17 (d, $J = 3.8$ Hz, 1H, H-4), 3.02 (d, $J = 13.5$ Hz, 1H, H-8), 3.12 (d, $J = 13.4$ Hz, 1H, H-8), 3.22 (s, 3H, OMe), 1.17 (m, 2H), 1.39 (m, 2H), 1.48 (m, 2H), 1.54 (m, 2H), 1.82 (m, 2H)(cyclohexyl), 3.23 (s, br., 1H, OH). ^{13}C NMR spectrum (100 MHz) in CDCl_3 , δ (ppm): 21.0 and 21.1 (C-9 and C-10), 23.9 (C-5), 28.0 (C-6), 47.5 (C-7), 49.9 (C-8), 51.0 (OMe), 55.8 (C-4), 64.1 (C-1), 72.9 (C-3), 194.5 (C-2), 22.8, 25.2 and 36.5 (cyclohexyl CH_2) and 74.0 (cyclohexyl C_q), 83.0 and 90.7 ($\text{C}\equiv\text{C}$).

Reduction pathway

(3a*S*,7a*S*)-8,8-Dimethyl-7-oxo-1,4,5,6,7,7a-hexahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (3-oxo-camphorsultam) (14).

To a well stirred solution of 3-oxo-camphorsulfonimide (**3**) (2.29 g, 10 mmol) in acetic acid (20 ml) and hot water (150 ml), zinc powder (1.4 g, 20 mmol) was added in small portions over a period of 1h. The reaction mixture was kept at 80 °C for another hour. Then, the excess of zinc powder was filtered off and the solvent was evaporated. The resulting white solid was extracted with chloroform to separate the organic material from the insoluble zinc salts. The filtrate was evaporated and the residue recrystallized from chloroform/diethyl ether.

Yield is 65 %. Anal. Calcd for $\text{C}_{10}\text{H}_{15}\text{NO}_3\text{S}$: C, 52.38; H, 6.59; N, 6.11, S, 13.98. Found: C, 52.24; H, 6.51; N, 6.19; S, 14.11. EI-MS, m/z : (M is 229.300) 229 [M] $^+$, 201 [$M - \text{CO}$] $^+$, 132 [$M - 97$] $^+$. M.p. 170 °C. IR spectrum (selected bands), cm^{-1} : 3180 w $\nu(\text{N-H})$, 1760 s $\nu(\text{C=O})$, 1310 and 1130 s $\nu(\text{SO}_2)$. ^1H NMR spectrum (400 MHz) in CDCl_3 , δ (ppm): 1.03 (s, 3H) and 1.15 (s, 3H)(9-H and 10-H), 1.73 (m, 1H), 1.84 (m, 1H) and 2.05-2.20 (m, 2H)(5-H and 6-H), 2.36 (d, $J = 3.8$ Hz, 1H, 4-H), 3.32 (d, $J = 13.8$ Hz, 1H) and 3.34 (d, $J = 13.8$ Hz, 1H)(8-H), 3.58 (d, $J = 4.3$ Hz, 1H, 2-H), 5.57 (d, $J = 4.3$ Hz, 1H, NH). ^{13}C NMR spectrum (100 MHz) in CDCl_3 , δ (ppm): 18.8 and 20.9 (C-9 and C-10), 20.4 and 30.85 (C-5 and C-6), 45.7 (C-7), 49.4 (C-8), 52.4 (C-1), 57.6 (C-4), 65.0 (C-2), 209.7 (C-3).

(3a*S*,7*R*,7a*S*)-7-Hydroxy-8,8-dimethyl-7-phenylethynyl-1,4,5,6,7,7a-hexahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (3-exo-hydroxy-3-endo-phenylethynyl-camphorsultam) (15).

Similar as described in [33], a solution of phenylacetylene (1.1 g, 10.8 mmol) in dry diethyl ether (10 ml) was cooled in an ice bath. Butyl lithium (1.6M in hexanes, 6.25 ml, 10 mmol) was added and the reaction mixture was left at room temperature for 30 min, before it was added dropwise to a suspension of 3-oxo-camphorsultam (**14**) (1.15 g, 5 mmol) in dry diethyl ether (10 ml). The reaction mixture was stirred overnight, water (10 ml) was added and the organic phase was separated. The aqueous phase was extracted twice with dichloromethane, and the combined organic phases were dried with Na₂SO₄. After chromatography on SiO₂ (eluent CH₂Cl₂/Et₂O 9:1) the compound was obtained as a white solid.

Yield is 72 %. Anal. Calcd for C₁₈H₂₁NO₃S: C, 65.23; H, 6.39; N, 4.23, S, 9.67. Found: C 65.17; H, 6.44; N, 4.11; S, 9.73. CI-MS, *m/z*: (M is 331.437) 332 [M + H]⁺. M.p. 74-76 °C. TLC on SiO₂, R_f = 0.48 (eluent CH₂Cl₂/Et₂O 9:1). IR spectrum (selected bands), cm⁻¹: 3292 s ν(N-H), 2218 w ν(C≡C), 1308 and 1133 s ν(SO₂). ¹H NMR spectrum (400 MHz) in CDCl₃, δ (ppm): 0.96 (s, 3H) and 1.35 (s, 3H)(9-H, 10-H), 1.45 (m, 1H), 1.86-1.94 (m, 2H) and 2.02 (m, 1H)(5-H and 6-H), 2.16 (d, J = 4.8 Hz, 1H, 4-H), 3.07 (s, br., 1H, OH), 3.19 (s, 2H, 8-H), 3.67 (d, J = 9.9 Hz, 2-H), 4.86 (d, J = 9.9 Hz, NH), 7.33 (m, 3H) and 7.43 (m, 2H)(Ph). ¹³C NMR spectrum (100 MHz) in CDCl₃, δ (ppm): 22.1 and 22.8 (C-9 and C-10), 23.8 and 30.3 (C-5 and C-6), 48.9 (C-7), 51.2 (C-8), 55.8 (C-4), 57.5 (C-1), 73.6 (C-2), 76.0 (C-3), 85.3 and 90.9 (C≡C), 121.7, 128.4, 128.8 and 131.7 (Ph).

Acetal pathway:

(3a*S*,7a*S*)-7,7-Dimethoxy-8,8-dimethyl-7a-phenylethynyl-1,4,5,6,7,7a-hexahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (2-endo-phenylethynyl-3,3-dimethoxy-camphorsultam) (17a).

Similar as described in [33], a solution of the phenylacetylene (520 mg, 5.1 mmol) in dry diethyl ether (10 ml) was cooled in an ice bath. Butyl lithium (1.6M in hexanes, 6.25 ml, 5 mmol) was added and the reaction mixture was left at room temperature for 30 min, before it was added dropwise to a suspension of 3,3-dimethoxy-camphorsulfonylimine (**16**) [18] (1.37 g, 5 mmol) in dry diethyl ether (10 ml). The reaction mixture was stirred overnight, water (10 ml) was added and the organic phase was separated. The aqueous phase was extracted twice with dichloromethane, and the combined organic phases were dried with Na₂SO₄. After chromatography on SiO₂ (eluent CH₂Cl₂/Et₂O 9:1) the compound was obtained as a colourless solid.

Yield is 82 %. Anal. Calcd for C₂₀H₂₅NO₄S: C, 63.98; H, 6.71; N, 3.73, S, 8.54. Found: C 64.08; H, 6.79; N, 3.67; S, 8.66. EI-MS, *m/z*: (M is 375.491) 375 [M]⁺, 360 [M - NH]⁺, 345 [M - OMe]⁺, 311 [M - SO₂]⁺, 183 [M - 192]⁺, 101 [PhCCH]⁺, 77 [Ph]⁺. M.p. 217 °C. TLC on SiO₂, R_f = 0.31 (eluent CH₂Cl₂). IR spectrum (selected bands), cm⁻¹: 3348 ν(NH), 2231 w ν(C≡C), 1307 and 1125 s ν (SO₂). ¹H NMR spectrum (500 MHz) in CDCl₃, δ (ppm): 0.99 (s, 3H) and 1.43 (s, 3H)(9-H, 10-H), 1.72-1.82 (m, 2H), 2.06 (m, 1H) and 2.36 (m, 1H)(5-H and 6-H), 2.23 (d, J = 4.8Hz, 1H, 4-H), 3.22 (d, J = 14.0 Hz, 1H) and 3.27 (d, J = 14.0 Hz, 1H)(8-H), 3.32 (s, 3H) and 3.41 (s, 3H)(2 OMe), 5.20 (s, 1H, NH), 7.27-7.33 (m, 3H) and 7.43-7.49 (m, 2H)(Ph). ¹³C NMR spectrum (125 MHz) in CDCl₃, δ (ppm): 21.7 and 23.1 (C-9 and C-10), 20.5 and 28.6 (C-5 and C-6), 46.6 (C-7), 49.3 (C-4), 50.0 (C-8), 50.9 and 51.2 (2 OMe), 63.4 (C-1), 70.8 (C-2), 86.7 and 88.2 (C≡C), 108.7 (C-3), 122.4, 128.1, 128.3 and 131.5 (Ph).

(3a*S*,7a*S*)-7,7-Diethoxy-8,8-dimethyl-7a-phenylethynyl-1,4,5,6,7,7a-hexahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (2-endo-phenylethynyl-3,3-diethoxy-camphorsultam) (17a').

The compound was prepared in analogy to **17a** from 3,3-diethoxy-camphorsulfonylimine (**16'**) [18] as a starting material. Yield is 77 %. Anal. Calcd for C₂₂H₂₉NO₄S: C, 65.48; H,

7.24; N, 3.47, S, 7.93. Found: C 65.08; H, 7.11; N, 3.55; S, 8.11. EI-MS, m/z : (M is 403.545) 404 $[M]^+$, 359 $[M - OEt]^+$, 340 $[M - SO_2]^+$, 101 $[PhCCH]^+$, 77 $[Ph]^+$. TLC on SiO_2 , $R_f = 0.33$ (eluent CH_2Cl_2). IR spectrum (selected bands), cm^{-1} : 3411 $\nu(NH)$, 2233 $\nu(C\equiv C)$, 1305 and 1123 $\nu(SO_2)$. 1H NMR spectrum (500 MHz) in $CDCl_3$, δ (ppm): 1.23 (t, 7.2 Hz, 6H, 2 OEt), 1.00 (s, 3H) and 1.43 (s, 3H)(9-H, 10-H), 1.73-1.84 (m, 2H), 2.06 (m, 1H) and 2.37 (m, 1H)(5-H and 6-H), 2.25 (d, $J = 4.8$ Hz, 1H, 4-H), 3.22 (d, $J = 14.0$ Hz, 1H) and 3.26 (d, $J = 14.0$ Hz, 1H)(8-H), 3.44 (m, 1H), 3.57 (m, 2H) and 3.95 (m, 1H)(2 OEt), 5.19 (s, 1H, NH), 7.29-7.33 (m, 3H) and 7.45-7.48 (m, 2H)(Ph). ^{13}C NMR spectrum (125 MHz) in $CDCl_3$, δ (ppm): 14.2 and 14.6 (2 OEt), 21.7 and 23.2 (C-9 and C-10), 20.5 and 28.6 (C-5 and C-6), 46.5 (C-7), 49.5 (C-4), 50.0 (C-8), 58.5 and 59.1 (2 OEt), 63.3 (C-1), 70.7 (C-2), 86.8 and 88.2 ($C\equiv C$), 108.7 (C-3), 122.4, 128.0, 128.1 and 131.4 (Ph).

(3a*S*,7a*S*)-7,7-Dimethoxy-8,8-dimethyl-7a-(1-heptynyl)-1,4,5,6,7,7a-hexahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (2-endo-heptynyl-3,3-dimethoxycamphorsultam) (17b).

The compound was prepared in analogy to **17a** by reaction of 3,3-dimethoxycamphorsulfonylimine (**16**) with 1-heptynyl lithium. Yield 41 %. Accurate EI-MS, m/z : Calcd for $C_{19}H_{32}NO_4S$ $[M + H]^+$: 370.2040. Found: 370.2047 (Delta [mmu] -0.7). EI-MS, m/z : 370 $[M + H]^+$, 338 $[M - MeOH]^+$, 306 $[M - SO_2]^+$, 279 $[M - MeOH - SO_2]^+$. IR spectrum (selected bands), cm^{-1} : 3360 $\nu(NH)$, 2252 $\nu(C\equiv C)$, 1306 and 1123 $\nu(SO_2)$. 1H NMR spectrum (500 MHz) in $CDCl_3$, δ (ppm): 0.90 (t, 3H, $J = 7.2$ Hz, 3H, heptynyl-7), 0.98 (s, 3H, H-10), 1.33 (m, 2H, heptynyl-6), 1.41 (m, 2H, heptynyl-5), 1.40 (s, 3H, H-9), 1.53 (quint., $J = 7.3$ Hz, 2H, heptynyl-4), 1.73 (m, 2H, H-5 exo and H-6 exo), 1.98 (m, 1H, H-5 endo), 2.27 (d, $J = 5.0$ Hz, 1H, H-4), 2.28 (t, $J = 7.3$ Hz, 2H, heptynyl-13), 2.31 (1H, m, H-6 endo), 3.18 (d, $J = 14.2$ Hz, 1H, H-8), 3.19 (d, $J = 14.2$ Hz, 1H, H-8), 3.28 (s, 3H, OMe exo), 3.35 (s, 3H, OMe endo), 5.01 (s, br., 1H, NH). ^{13}C NMR spectrum (125 MHz) in $CDCl_3$, δ (ppm): 14.2 (CH_3 , heptynyl-7), 19.2 (CH_2 , heptynyl-3), 20.8 (CH_2 , C-5), 22.2

(CH₃, C-9), 22.3 (CH₂, heptynyl-6), 23.6 (CH₃, C-10), 28.2 (CH₂, heptynyl-4), 29.0 (CH₂, C-6), 31.2 (CH₂, heptynyl-5), 46.7 (C_q, C-7), 49.7 (CH, C-4), 50.4 (CH₂, C-8), 51.2 (CH₃, OMe exo), 51.5 (CH₃, OMe endo), 63.7 (C_q, C-1), 70.9 (C_q, C-2), 77.7 (C_q) and 89.7 (C_q)(C≡C), 108.8 (C_q, C-3).

(3a*S*,7a*S*)-8,8-Dimethyl-7-oxo-7a-phenylethynyl-1,4,5,6,7,7a-hexahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (12a).

To a solution of **17a** or **17a'** (4 mmol) in acetone (5 ml), conc. HCl (0.05 ml) was added and the reaction mixture was stirred at room temperature overnight. After evaporation of the solvent and chromatography (SiO₂, CH₂Cl₂/Et₂O 9:1), the compound was obtained as a colourless solid. Yield is 91 % (from **17a**); 82 % (from **17a'**). For analytical data of product **12a**, see above.

(3a*S*,7a*S*)-8,8-Dimethyl-7-oxo-7a-(1-heptynyl)-1,4,5,6,7,7a-hexahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (12b).

This compound was prepared in analogy to **12a** from **17b** as starting material. Colourless oil. Yield 81 %. For analytical data of product **12b**, see above.

(3a*S*,7*R*,7a*S*)-7-Hydroxy-8,8-dimethyl-7a-phenylethynyl-1,4,5,6,7,7a-hexahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (2-endo-phenylethynyl-3-exo-hydroxy-camphorsultam) (18).

A solution of **12a** (200 mg, 0.61 mmol) in ethanol (5 ml) was cooled to 0 °C. Then, solid NaBH₄ (28 mg, 0.74 mmol) was added, the ice bath was removed and the reaction mixture stirred at room temperature for 15 min. Water (5 ml) was added and the reaction mixture was heated to reflux for 15 min. The mixture was extracted with diethylether (5 ml) and then with CH₂Cl₂ (2 × 3 ml) and the organic phase was dried over MgSO₄. After evaporation of the solvent and chromatography (SiO₂, CH₂Cl₂/Et₂O 9:1) the product was obtained as a colourless solid.

Yield is 86 %. Accurate EI-MS, m/z : Calcd for $C_{18}H_{20}NO_3S$ $[M - H]^+$: 330.1164. Found: 330.1174 (Δ [mmu] -1.0). EI-MS, m/z : (M is 331.437) 331 $[M]^+$, 330 $[M - H]^+$, 267 $[M - SO_2]^+$, 102 $[PhCCH]^+$. M.p. 202-203 °C. TLC on SiO_2 , $R_f = 0.42$ (CH_2Cl_2/Et_2O 9:1). IR spectrum (selected bands), cm^{-1} : 3524 and 3452 s $\nu(O-H)$, 3350 and 3297 $\nu(N-H)$, 2217 w $\nu(C\equiv C)$, 1305 and 1128 s $\nu(SO_2)$. 1H NMR spectrum (500 MHz) in $CDCl_3$, δ (ppm): 0.99 (s, 3H, 9/10-H), 1.44 (s, 3H, 9/10-H), 1.34 (m, 1H, 5-H endo), 1.81 (m, 1H, 6-H endo), 1.92 (m, 1H, 5-H exo), 2.23 (m, 1H, 6-H exo), 2.02 (d, $J = 5.2$ Hz, 1H, 4-H), 2.69 (d, $J = 6.0$ Hz, 1H, OH), 3.32 (d, $J = 13.6$ Hz, 1H, H-8), 3.40 (d, $J = 13.6$ Hz, 1H, H-8), 4.31 (d, $J = 6.4$ Hz, 1H, H-3 endo), 4.97 (s, 1H, NH), 7.31 (m, 3H) and 7.44 (m, 2H)(Ph). ^{13}C NMR spectrum (125 MHz) in $CDCl_3$, δ (ppm): 22.8 (CH_3) and 23.4 (CH_3)(C-9,C-10), 24.4 (CH_2 , C-5), 28.5 (CH_2 , C-6), 49.4 (C_q , C-7), 51.3 (CH_2 , C-8), 51.4 (CH , C-4), 61.6 (C_q , C-1), 68.7 (C_q , C-2), 85.6 (CH , C-3), 86.9 and 89.6 ($C\equiv C$), 122.3 (C_q), 128.5, 128.9 and 132.1(CH)(Ph).

Imine pathway:

(3a*S*)-8,8-Dimethyl-7-(2-phenylethyl)imino-4,5,6,7-tetrahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (3-((2-phenylethyl)imino)-camphorsulfonylimine) (19) [40].

A solution of 3-oxo-camphorsulfonylimine (**3**) (10.6 g, 50 mmol) and 2-phenylethylamine (21.2 g, 175 mmol) in toluene (200 ml) was cooled to 0 °C. A solution of $TiCl_4$ (6.5 g, 25 mmol) in toluene (50 ml) was added dropwise. The reaction mixture was refluxed for 16 h and then cooled to room temperature. Chloroform (250 ml) was added and the mixture stirred for 2 h. After filtration, activated charcoal (2 g) was added to the filtrate. After stirring for 10 minutes, the charcoal was filtered off over a bed of Celite, the solvent was evaporated and the residual solid recrystallised from chloroform/diethyl ether.

Yield is 61.7 %. Accurate EI-MS, m/z : Calcd for $C_{18}H_{22}N_2O_2S$ $[M]^+$: 330.1402. Found: 330.1418 (Δ [mmu] -1.6). EI-MS, m/z : (M is 330.452) 330 $[M]^+$, 266 $[M - SO_2]^+$, 105

$[\text{PhCH}_2\text{CH}_2]^+$. M.p. 148-150 °C. TLC on SiO_2 , $R_f = 0.66$ (eluent ethyl acetate/hexane 2:1). IR spectrum (selected bands), cm^{-1} : 1675 and 1647 s $\nu(\text{C}=\text{N})$, 1336 and 1160 s $\nu(\text{SO}_2)$. ^1H NMR spectrum (500 MHz) in CDCl_3 , δ (ppm): 0.65 (s, 3H) and 1.01 (s, 3H)(9-H, 10-H), 1.09 (m, 1H, H-5 endo), 1.77 (m, 1H, H-6 endo), 1.95 (m, 1H, H-5 exo), 2.06 (m, 1H, H-6 exo), 2.85 (d, $J = 4.8$ Hz, H-4), 3.07 (d, $J = 12.0$ Hz, 1H) and 3.28 (d, $J = 12.0$ Hz, 1H)(H-8), 3.09 (m, 2H, CH_2Ph), 3.91 (m, 2H, $\text{CH}_2\text{N}=\text{}$), 7.21 (m, 3H) and 7.26 (m, 2H)(Ph). ^{13}C NMR spectrum (125 MHz) in CDCl_3 , δ (ppm): 18.3 and 19.4 (C-9 and C-10), 23.1 (C-5), 28.3 (C-6), 36.3 (CH_2Ph), 46.0 (C-7), 49.6 (C-4), 49.7 (C-8), 57.2 ($\text{CH}_2\text{N}=\text{}$), 62.6 (C-1), 126.4, 128.4, 128.9 and 139.4 (Ph), 167.0 (C-3), 185.0 (C-2).

(3a*S*,7a*S*)-8,8-Dimethyl-7-(2-phenylethyl)imino-7a-phenylethynyl-1,4,5,6,7,7a-hexahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (20).

Similar as described in [33], a solution of phenylacetylene (520 mg, 5.1 mmol) in dry diethyl ether (10 ml) was cooled in an ice bath. Butyl lithium (1.6M in hexanes, 6.25 ml, 5 mmol) was added dropwise and the reaction mixture was left at room temperature for 30 min, before it was added dropwise to a suspension of 3-((2-phenylethyl)imino)-camphorsulfonylimine (**19**) (1.65 g, 5 mmol) in dry diethyl ether (10 ml). The reaction mixture was stirred overnight, water (10 ml) was added and the organic phase was separated. The aqueous phase was extracted twice with dichloromethane, and the combined organic phases were dried with Na_2SO_4 . After chromatography on SiO_2 (eluent $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ 9:1) the compound was obtained as a pale yellow solid.

Yield is 78 %. Accurate EI-MS, m/z : Calcd for $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_2\text{S}$ $[\text{M} - \text{H}]^+$: 431.1793. Found: 431.1793 (Δ [mmu] 0.0). EI-MS, m/z : (M is 432.589) 432 $[\text{M}]^+$, 431 $[\text{M} - \text{H}]^+$, 368 $[\text{M} - \text{SO}_2]^+$, 328 $[\text{M} - \text{PhCH}=\text{CH}_2]^+$, 264 $[\text{M} - \text{SO}_2 - \text{PhCH}=\text{CH}_2]^+$, 105 $[\text{PhCH}_2\text{CH}_2]^+$, 102 $[\text{PhCCH}]^+$. M.p. 87-88 °C. TLC on SiO_2 , $R_f = 0.56$ (eluent ethyl acetate/hexane 2:1). IR spectrum (selected bands), cm^{-1} : 3195 s $\nu(\text{N}-\text{H})$, 2221 w $\nu(\text{C}\equiv\text{C})$, 1695 s $\nu(\text{C}=\text{N})$, 1309 and 1144 s $\nu(\text{SO}_2)$. ^1H NMR spectrum (500 MHz) in CDCl_3 , δ (ppm): 1.00 (s, 3H, H-10),

1.14 (s, 3H, H-9), 1.02 (m, 1H, H-5 endo), 1.73 (m, 1H, H-5 exo), 1.91 (td, J = 12.0 Hz, J = 6.0 Hz, 1H, H-6 exo), 2.36 (m, 1H, H-6 endo), 2.91 (m, 1H) and 3.00 (m, 1H)(CH₂Ph), 2.71 (d, J = 4.6 Hz, 1H, H-4), 3.30 (d, J = 12.2 Hz, 1H, H-8 syn), 3.37 (d, J = 12.2 Hz, 1H, H-8 anti), 3.67 (m, 1H) and 3.76 (m, 1H)(CH₂N=), 7.21 (m, 3H) and 7.26 (m, 2H)(CH₂Ph), 7.15 (m, 1H), 7.30 (m, 2H) and 7.47 (d, 8.2 Hz, 2H)(PhC≡C). ¹³C NMR spectrum (125 MHz) in CDCl₃, δ (ppm): 20.2 (C-10), 22.6 (C-5), 22.8 (C-9), 29.5 (C-6), 36.8 (CH₂Ph), 46.7 (C-7), 48.9 (C-4), 50.0 (C-8), 55.4 (CH₂N=), 57.6 (C-1), 66.1 (C-2), 87.3 and 88.0 (C≡C), 122.5, 126.5, 128.4 and 128.6 (CH₂Ph), 128.9, 129.4, 132.2 and 140.0 (PhC≡C), 175.8 (C-3).

(3a*S*,7a*S*)-8,8-Dimethyl-7-oxo-7a-phenylethynyl-1,4,5,6,7,7a-hexahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (12a).

To a suspension of **20** (107 mg, 0.25 mmol) in water (5 ml), conc. HCl (0.5 ml) was added and the reaction mixture was refluxed overnight. The reaction mixture was left to cool and the crude product was collected by filtration. The product was purified by chromatography (SiO₂, CH₂Cl₂/Et₂O 9:1) and obtained as a colourless solid. Yield is 38 %. For analytical data of product **12a**, see above.

Bis-Alkyne Derivatives:

(3a*S*,7*R*,7a*S*)-8,8-Dimethyl-7-heptynyl-7-hydroxy-7a-phenylethynyl-1,4,5,6,7,7a-hexahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (2-endo-phenylethynyl-3-endo-heptynyl-3-exo-hydroxy-camphorsultam) (21a).

Similar as described in [33], a solution of 1-heptyne (395 mg, 4.1 mmol) in dry diethyl ether (5 ml) was cooled in an ice bath. Butyl lithium (1.6M in hexanes, 2.5 ml, 4 mmol) was added and the reaction mixture was left at room temperature for 30 min, before it was added dropwise to a suspension of **12a** (660 mg, 2 mmol) in dry diethyl ether (5 ml). The reaction mixture was refluxed overnight, water (10 ml) was added and the organic phase was separated. The aqueous phase was extracted twice with dichloromethane, and the

combined organic phases were dried with Na₂SO₄. After chromatography on SiO₂ (eluent CH₂Cl₂/Et₂O 9:1) the compound was obtained as a white solid.

Yield 76 %. Elemental analysis calculated for C₂₅H₃₁NO₃S: C 70.55; H 7.34; N 3.29; found: C 70.44; H 7.69; N 3.10. EI-MS: (M = 425.595) 426 [M + H]⁺, 408 [M – H₂O]⁺, 330 [M – heptyne]⁺, 324 [M – PhC≡CH]⁺. IR spectrum (selected bands), cm⁻¹: 3411 s ν(OH), 3323 ν(NH), 2233 w ν(C≡C), 1335 and 1149 s ν(SO₂). ¹H NMR spectrum (500 MHz) in CDCl₃, δ (ppm): 0.73 (t, 7.5 Hz, 3H, heptynyl-7), 0.95 (s, 3H, H-10), 1.13 (m, 2H, heptynyl-6), 1.22 (m, 2H, heptynyl-5), 1.38 (m, 2H, heptynyl-4), 1.41 (s, 3H, H-9), 1.71 (m, 1H, H-6 exo), 1.79 (m, 1H, H-5 exo), 1.97 (m, 1H, H-5 endo), 2.03 (d, J = 5.1 Hz, 1H, H-4), 2.16 (t, J = 7.2 Hz, 2H, heptynyl-3), 2.19 (m, 1H, H-6 endo), 2.87 (s, br., 1H, OH), 3.25 (d, J = 13.5 Hz, 1H, H-8 syn), 3.30 (d, J = 13.5 Hz, 1H, H-8 anti), 5.08 (s, 1H, NH), 7.22 (m, 3H, *m*- and *p*-Ph), 7.40 (m, 2H, *o*-Ph). ¹³C NMR spectrum (125 MHz) in CDCl₃, δ (ppm): 14.1 (CH₃, heptynyl-7), 19.0 (CH₂, heptynyl-3), 22.3 (CH₂, heptynyl-6), 23.8 (CH₃, C-9), 24.2 (CH₂, C-5), 24.3 (CH₃, C-10), 28.4 (CH₂, heptynyl-4), 28.6 (CH₂, C-6), 31.4 (CH₂, heptynyl-5), 49.2 (C_q, C-7), 51.6 (CH₂, C-8), 56.7 (CH, C-4), 62.8 (C_q, C-1), 73.1 (C_q, C-2), 82.2 (C_q, C-3), 80.7, 88.0, 89.7 and 90.2 (C_q, C≡C), 122.8 (C_q, Ph), 128.4 (CH, *m*-Ph), 128.8 (CH, *p*-Ph), 131.9 (CH, *o*-Ph).

(3a*S*,7*R*,7a*S*)-8,8-Dimethyl-7a-heptynyl-7-hydroxy-7-phenylethynyl-1,4,5,6,7,7a-hexahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (2-endo-heptynyl-3-endo-phenylethynyl-3-exo-hydroxy-camphorsultam) (21b).

This compound was prepared in analogy to **21a** from **12b** and phenylethynyl lithium as starting materials.

Yield 73 %. Accurate EI-MS, *m/z*: Calcd for C₂₅H₃₂NO₃S [M + H]⁺: 426.2097. Found: 426.2095 (Δ [mmu] -0.2). EI-MS, *m/z*: 426 [M + H]⁺, 408 [M – H₂O]⁺, 362 [M – SO₂]⁺, 345 [M – H₂O – SO₂]⁺. IR spectrum (selected bands), cm⁻¹: 3414 ν(OH), 3322 s ν(NH), 2235 w ν(C≡C), 1330 and 1128 s ν(SO₂). ¹H NMR spectrum (500 MHz) in CDCl₃, δ

(ppm): 0.78 (t, 7.3 Hz, 3H, heptynyl-7), 1.02 (s, 3H, H-10), 1.17 (m, 2H, heptynyl-6), 1.28 (m, 2H, heptynyl-5), 1.48 (s, 3H, H-9), 1.54 (m, 2H, heptynyl-4), 1.76 (td, $J = 12.2$ Hz, $J = 5.0$ Hz, 1H, H-6 exo), 1.89 (m, 1H, H-5 exo), 2.04 (ddd, $J = 13.8$ Hz, $J = 9.2$ Hz, $J = 4.8$ Hz, 1H, H-5 endo), 2.18 (d, $J = 4.9$ Hz, 1H, H-4), 2.22 (m, 1H, H-6 endo), 2.27 (t, $J = 7.2$ Hz, 2H, heptynyl-3), 3.16 (s, br., 1H, OH), 3.29 (d, $J = 13.7$ Hz, 1H, H-8 syn), 3.33 (d, $J = 13.7$ Hz, 1H, H-8 anti), 5.08 (s, 1H, NH), 7.31 (m, 3H, *m*- and *p*-Ph), 7.45 (m, 2H, *o*-Ph). ^{13}C NMR spectrum (125 MHz) in CDCl_3 , δ (ppm): 14.1 (CH_3 , heptynyl-7), 19.2 (CH_2 , heptynyl-3), 22.3 (CH_2 , heptynyl-6), 23.9 (CH_3 , C-9), 24.1 (CH_2 , C-5), 24.3 (CH_3 , C-10), 28.4 (CH_2 , heptynyl-4), 28.6 (CH_2 , C-6), 31.3 (CH_2 , heptynyl-5), 49.1 (C_q , C-7), 51.5 (CH_2 , C-8), 56.7 (CH, C-4), 62.2 (C_q , C-1), 72.9 (C_q , C-2), 78.4 (C_q , heptynyl-1), 82.4 (C_q , C-3), 88.1 (C_q) and 89.9 (C_q)($\text{PhC}\equiv\text{C}$), 91.8 (C_q , heptynyl-2), 122.5 (C_q , Ph), 128.6 (CH, *m*-Ph), 128.9 (CH, *p*-Ph), 131.9 (CH, *o*-Ph).

Platinum-catalysed Cycloisomerisations:

A solution of **21a** (150mg, 0.35 mmol) and $\text{PtCl}_2(\text{PhCN})_2$ (8 mg, 0.017 mmol, 5 mol %) in CHCl_3 (2 ml) was heated to 60 °C overnight. Alternatively, the reaction mixture was heated under microwave irradiation to 80 °C for 30 min in a sealed vial. The initial pale yellow colour of the solution changed to orange-brownish. The solvent was evaporated and the residue was purified by column chromatography on SiO_2 (eluent $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$, gradient ratios 10:0, 10:1, 10:2, 10:5).

(2*S*, 3*aS*)-10-Benzoyl-11,11-dimethyl-9-pentyl-4,5,6,7-tetrahydro-1*H*,3*H*-3*a*,6-methanocyclonona[2,1-*c*]isothiazol-7-one 2-oxide (**22a**).

Yield 67 %. Elemental analysis calculated for $\text{C}_{25}\text{H}_{31}\text{NO}_3\text{S}$: C 70.55; H 7.34; N 3.29; found: C 70.10; H 7.19; N 3.26. Accurate EI-MS, m/z : Calcd for $\text{C}_{25}\text{H}_{32}\text{NO}_3\text{S}$ $[\text{M} + \text{H}]^+$: 426.2097. Found: 426.2091 (Δ [mmu] -0.6). EI-MS, m/z : 426 $[\text{M} + \text{H}]^+$, 410 $[\text{M} - \text{NH}_3]^+$, 377 $[\text{M} - \text{SO}]^+$. IR spectrum (selected bands), cm^{-1} : 3110 w $\nu(\text{N-H}\cdots\text{O}=\text{O})$, 1680 and 1611 s $\nu(\text{C}=\text{O})$, 1533 s $\nu(\text{C}=\text{C})$, 1098 m $\nu(\text{SO})$. ^1H NMR spectrum (500 MHz) in CDCl_3 , δ

(ppm): 0.76 (t, $J = 7.1$ Hz, 3H, pentyl-5), 0.99 (m, 2H, pentyl-3), 1.08 (m, 2H, pentyl-4), 1.30 (m, 2H, pentyl-2), 1.32 (s, 3H, H-10), 1.35 (s, 3H, H-9), 1.70 (m, 1H, pentyl-1), 1.76 (m, 1H, pentyl-1), 1.97 (m, 1H, H-5 endo), 2.15 (m, 1H, H-6 exo), 2.22 (m, 1H, H-5 exo), 2.62 (d, $J = 6.1$ Hz, 1H, H-4), 2.74 (m, 1H, H-6 endo), 3.08 (d, $J = 14.1$ Hz, 1H, H-8 anti), 3.50 (d, $J = 14.1$ Hz, 1H, H-8 syn), 5.94 (s, 1H, =CH), 7.38 (t, $J = 7.2$ Hz, 2H, *m*-Ph), 7.45 (t, $J = 7.4$ Hz, 1H, *p*-Ph), 7.65 (d, $J = 7.8$ Hz, 2H, *o*-Ph), 11.97 (s, 1H, NH). ^{13}C NMR spectrum (125 MHz) in CDCl_3 , δ (ppm): 14.1 (CH_3 , pentyl-5), 22.0 (CH_3 , C-9), 22.4 (CH_2 , pentyl-4), 25.4 (CH_2 , C-5), 27.6 (CH_2 , pentyl-2), 28.9 (CH_3 , C-10), 31.5 (CH_2 , pentyl-3), 35.6 (CH_2 , C-6), 39.4 (CH_2 , pentyl-1), 47.1 (C_q , C-7), 60.3 (CH_2 , C-8), 61.5 (C_q , C-1), 66.8 (CH , C-4), 109.0 (C_q , C2=C=), 128.27 (CH) and 128.28 (CH)(*o*- and *m*-Ph), 129.3 (CH , =CH), 131.8 (CH , *p*-Ph), 138.4 (C_q , HC=C=), 140.5 (C_q , Ph), 163.4 (C_q , C-2), 198.3 (C_q , Ph-C=O), 210.8 (C_q , C-3).

(2*S*, 3*aS*)-11,11-Dimethyl-10-(1-oxohexyl)-9-phenyl-4,5,6,7-tetrahydro-1*H*,3*H*-3*a*,6-methanocyclonona[2,1-*c*]isothiazol-7-one 2-oxide (22b).

This compound was prepared in analogy to **22a** from **21b** as starting material. The reaction provided **22b** and **23** as a 1:1 mixture. These products were separated by column chromatography on SiO_2 (eluent ethyl acetate/hexane 1:1).

Yield 37 %. Elemental analysis calculated for $\text{C}_{25}\text{H}_{31}\text{NO}_3\text{S}$: C 70.55; H 7.34; N 3.29; found: C 70.29; H 7.24; N 3.23. Accurate EI-MS, m/z : Calcd for $\text{C}_{25}\text{H}_{32}\text{NO}_3\text{S}$ $[\text{M} + \text{H}]^+$: 426.2093. Found: 426.2091 (Δ [mmu] -0.4). EI-MS, m/z : 426 $[\text{M} + \text{H}]^+$, 377 $[\text{M} - \text{SO}]^+$. $R_f = 0.35$ (eluent ethyl acetate/hexane 1:1). IR spectrum (selected bands), cm^{-1} : 3105 w $\nu(\text{N-H}\cdots\text{O}=\text{O})$, 1695 and 1623 s $\nu(\text{C}=\text{O})$, 1533 s $\nu(\text{C}=\text{C})$, 1100 m $\nu(\text{SO})$. ^1H NMR spectrum (500 MHz) in CDCl_3 , δ (ppm): 0.75 (t, $J = 7.2$ Hz, 3H, pentyl-5), 0.96 (m, 2H, pentyl-3), 1.10 (m, 2H, pentyl-4), 1.13 (m, 1H, pentyl-2), 1.27 (s, 3H, H-9), 1.30 (s, 3H, H-10), 1.40 (m, 1H, pentyl-2), 1.89 (ddd, $J = 15.8$ Hz, $J = 8.6$ Hz, $J = 6.0$ Hz, 1H, pentyl-1), 2.28 (ddd, $J = 15.8$ Hz, $J = 8.6$ Hz, $J = 6.1$ Hz, 1H, pentyl-1), 1.97 (m, 1H, H-5 endo),

2.08 (m, 1H, H-6 exo), 2.18 (m, 1H, H-5 exo), 2.61 (d, J = 5.9 Hz, 1H, H-4), 2.64 (m, 1H, H-6 endo), 3.09 (d, J = 14.2 Hz, 1H, H-8 anti), 3.47 (d, J = 14.2 Hz, 1H, H-8 syn), 6.60 (s, 1H, =CH), 7.34 (m, 5H, Ph), 12.76 (s, 1H, NH). ¹³C NMR spectrum (125 MHz) in CDCl₃, δ (ppm): 14.1 (CH₃, pentyl-5), 21.9 (CH₃, C-9), 22.3 (CH₂, pentyl-4), 25.4 (CH₂, C-5), 24.8 (CH₂, pentyl-2), 28.6 (CH₃, C-10), 31.2 (CH₂, pentyl-3), 34.8 (CH₂, C-6), 41.7 (CH₂, pentyl-1), 47.6 (C_q, C-7), 59.5 (CH₂, C-8), 61.5 (C_q, C-1), 66.7 (CH, C-4), 107.5 (C_q, C2-C=), 126.6 (CH) and 129.4 (CH)(*o*- and *m*-Ph), 128.9 (CH, *p*-Ph), 131.4 (CH, =CH), 136.9 (C_q, HC=C), 141.5 (C_q, Ph), 163.6 (C_q, C-2), 204.9 (C_q, pentyl-C=O), 209.4 (C_q, C-3).

(3R,4aS,7S,7aR,9bS)-5,6,7,7a-Tetrahydro-7a-hydroxy-11,11-dimethyl-1-pentyl-9-phenyl-4H-4a,7-methanoindeno[7,1-de][1,2]oxathiepin-3,9b-imine 3-oxide (23).

Yield 37 %. Accurate ESI-MS, m/z: Calcd for C₂₅H₃₁NNaO₃S [M + Na]⁺: 448.1915. Found: 448.1917 (Δ [mmu] 0.2). ESI-MS: (M = 425.595) 448 [M + Na]⁺. R_f = 0.75 (eluent ethyl acetate/hexane 1:1). IR spectrum (selected bands), cm⁻¹: 3303 s ν(OH), 1653 m ν(C=C), 1324 and 1059 s ν(SON). ¹H NMR spectrum (500 MHz) in CDCl₃, δ (ppm): 0.76 (t, 7.1 Hz, 3H, pentyl-5), 0.95 (m, 2H, pentyl-3), 0.97 (s, 3H, H-9 or H-10), 1.08 (m, 2H, pentyl-4), 1.10 (m, 2H, pentyl-2), 1.43 (s, 3H, H-10 or H-9), 1.50 (m, 1H, H-5 endo), 1.72 (m, 1H, H-6 exo), 1.75 (m, 2H, pentyl-1), 1.78 (m, 1H, H-5 exo), 1.90 (m, 1H, H-6 endo), 2.11 (d, J = 5.8 Hz, 1H, H-4), 2.76 (s, 1H, OH), 3.07 (d, J = 14.0 Hz, 1H, H-8 anti or syn), 3.43 (d, J = 14.0 Hz, 1H, H-8 syn or anti), 5.80 (s, 1H, =CH), 7.23 (m, 2H, *o*-Ph), 7.34 (m, 3H, *m*- and *p*-Ph). ¹³C NMR spectrum (125 MHz) in CDCl₃, δ (ppm): 14.1 (CH₃, pentyl-5), 22.4 (CH₂, pentyl-4), 22.5 (CH₃, C-9 or C-10), 23.2 (CH₃, C-10 or C-9), 24.8 (CH₂, C-5), 26.7 (CH₂, pentyl-2), 27.7 (CH₂, C-6), 31.3 (CH₂, pentyl-3), 30.2 (CH₂, pentyl-1), 51.2 (C_q, C-7), 52.3 (CH₂, C-8), 53.2 (CH, C-4), 60.6 (C_q, C-1), 84.0 (C_q, C-2), 90.0 (C_q, C-3), 125.5 (C_q, C2-C=), 128.2 (2 CH, *o*- and *p*-Ph), 128.5 (CH, *m*-Ph), 136.0 (C_q, CH=C), 138.5 (CH, =CH), 140.1 (C_q, Ph), 151.4 (C_q, =C-O).

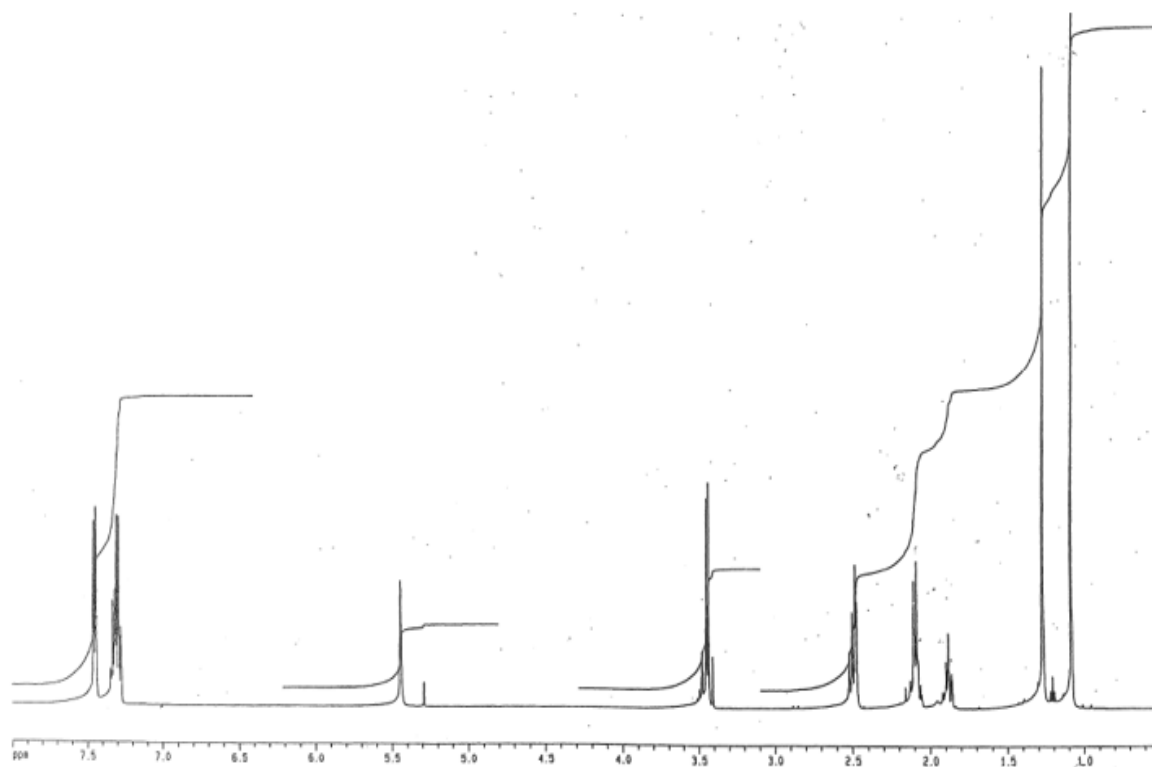
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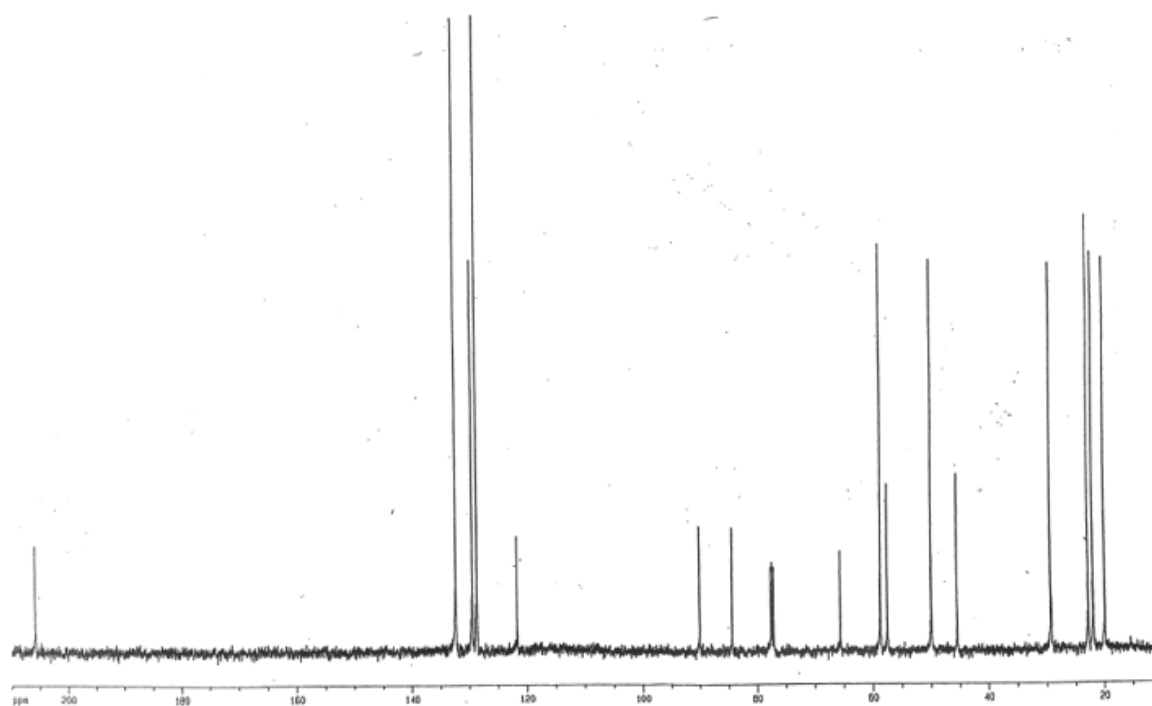
^1H and ^{13}C NMR spectra of compounds

12a, 12b, 13a, 17a, 17b, 18, 19, 20, 21a, 21b, 22a, 22b and 23

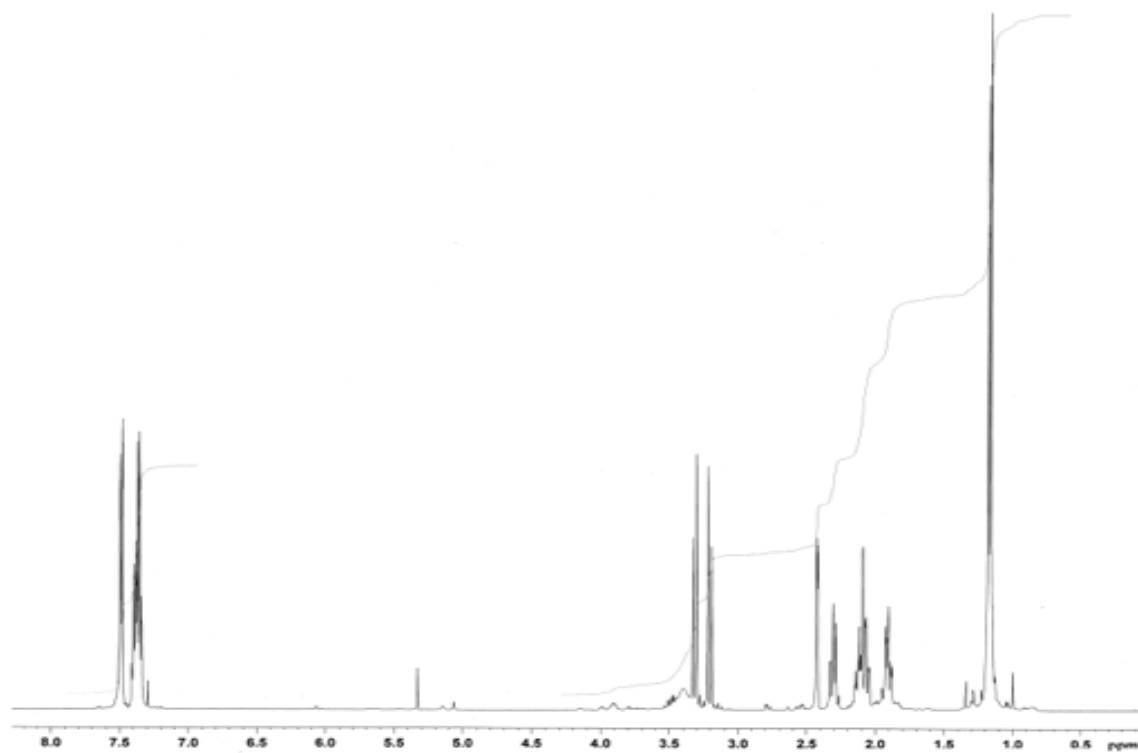
^1H NMR spectrum (500 MHz) of compound 12a



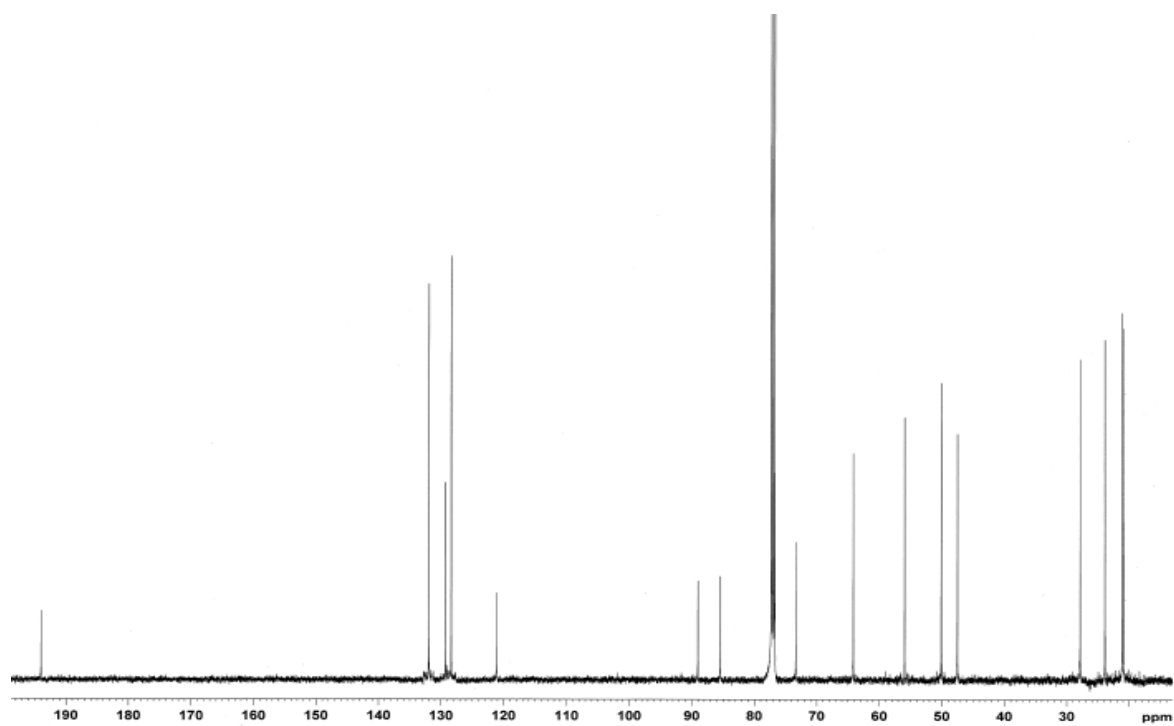
^{13}C NMR spectrum (125 MHz) of compound 12a



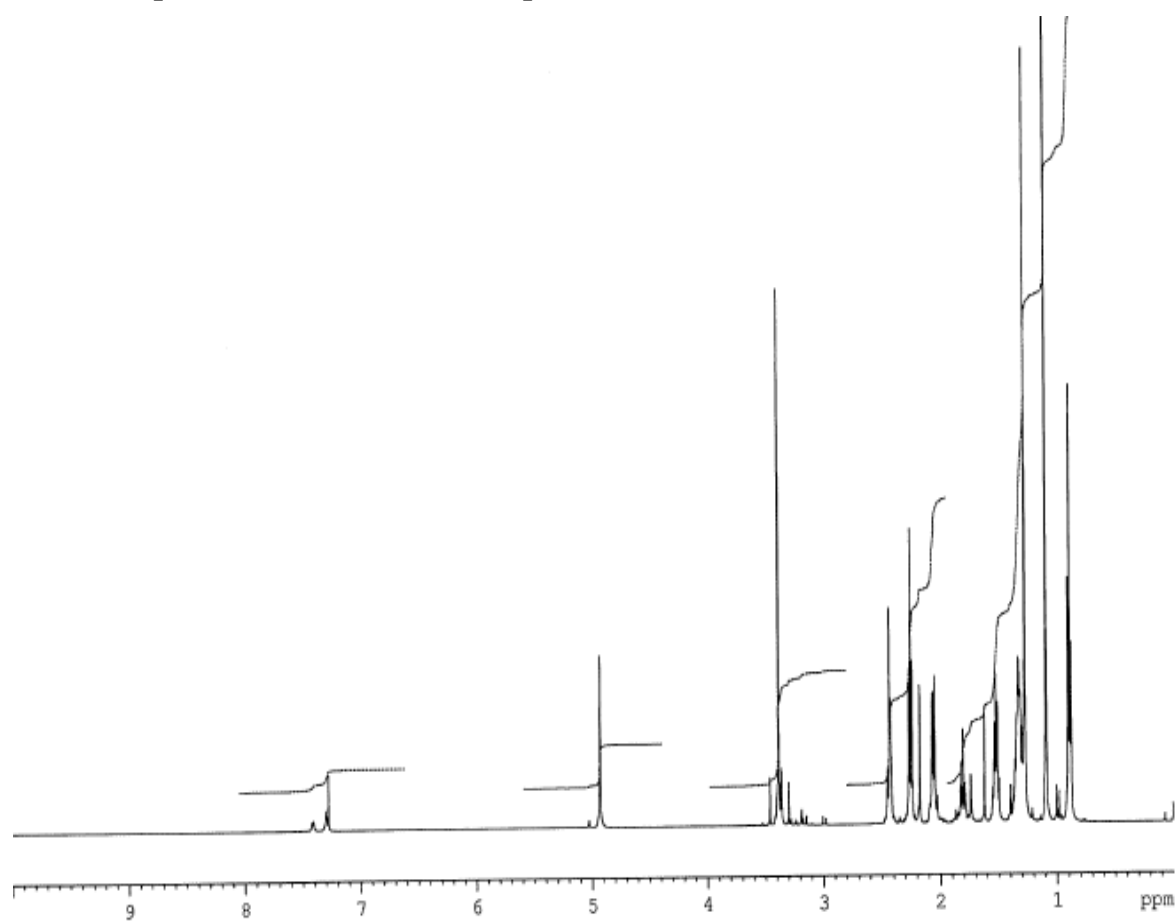
^1H NMR spectrum (500 MHz) of compound 13a



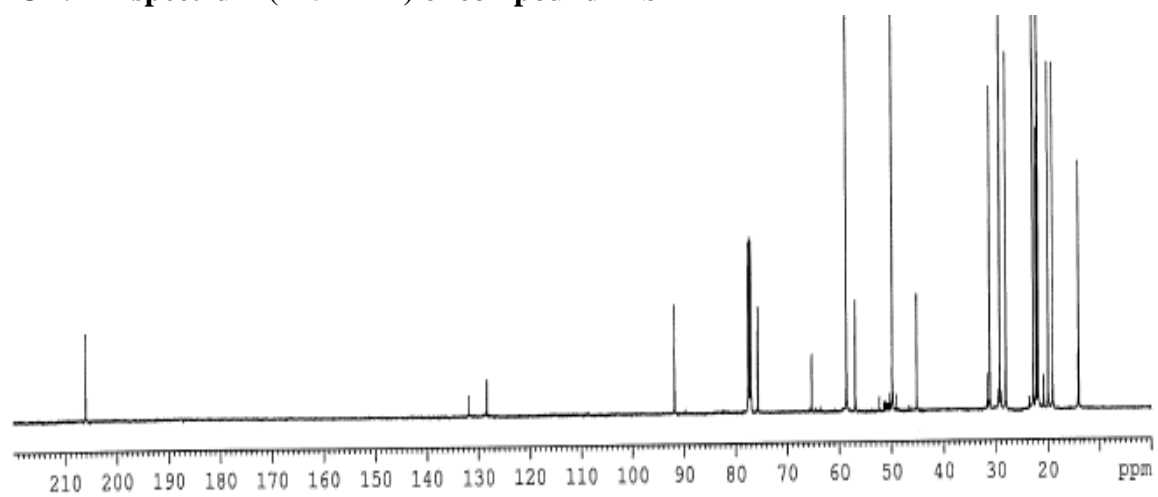
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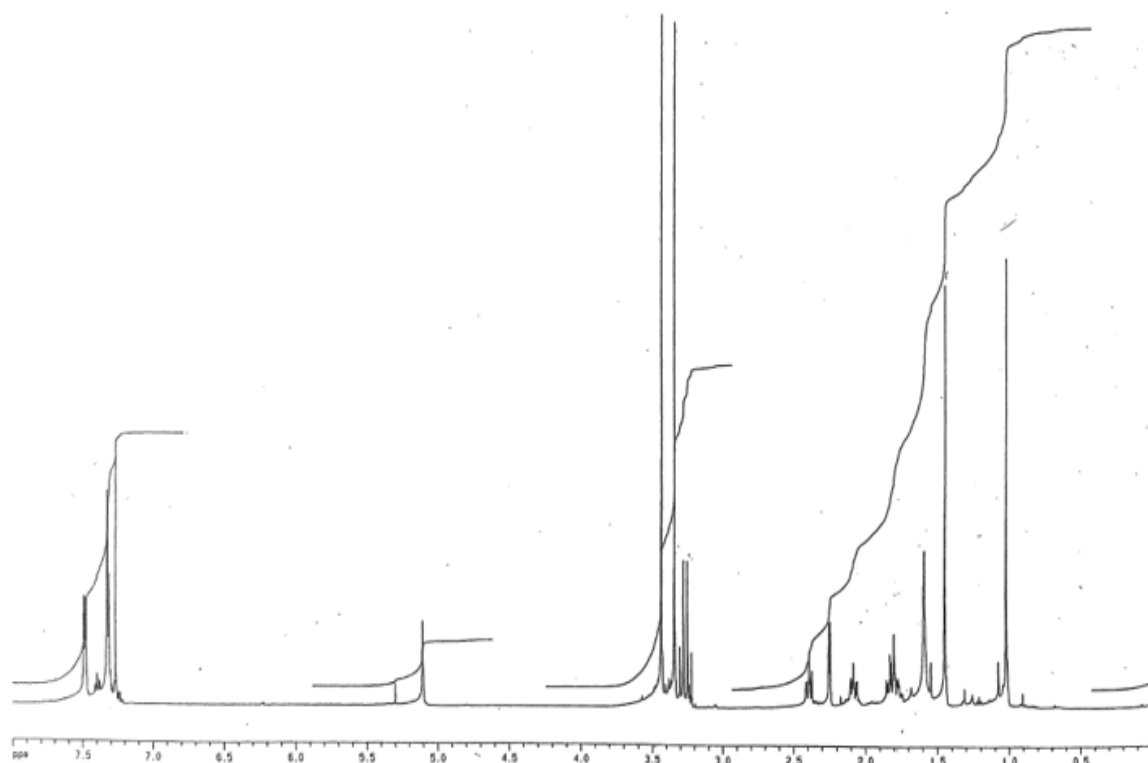
^1H NMR spectrum (500 MHz) of compound 12b



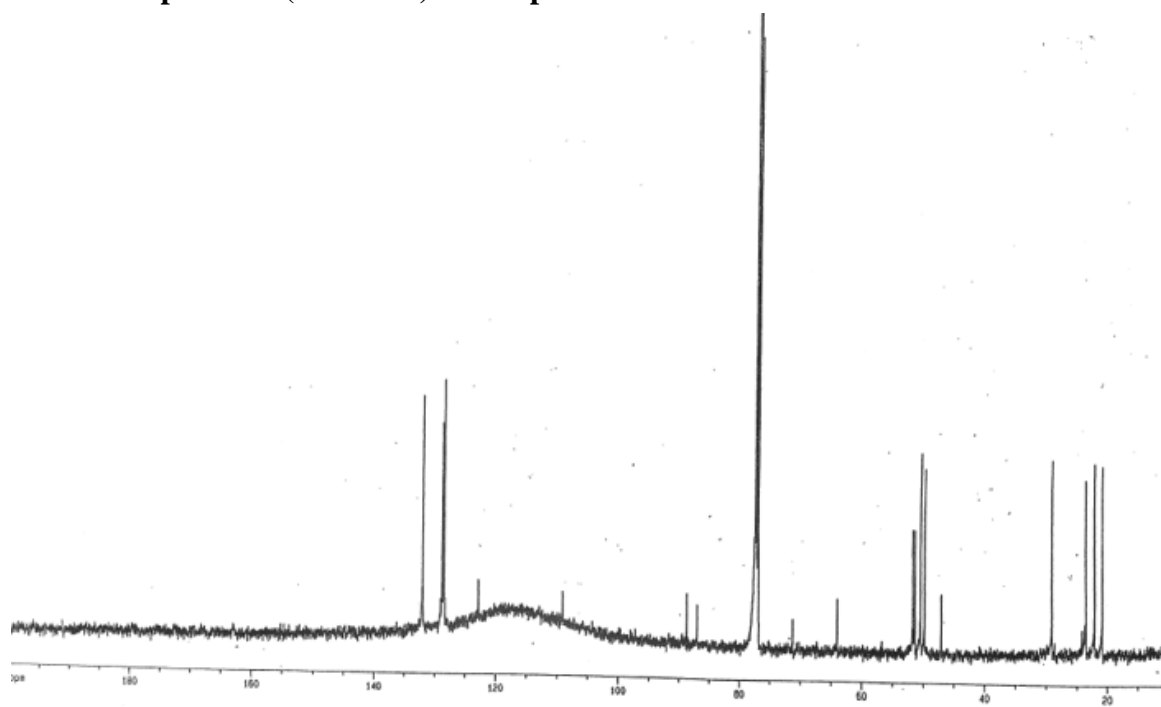
^{13}C NMR spectrum (125 MHz) of compound 12b



^1H NMR spectrum (500 MHz) of compound 17a



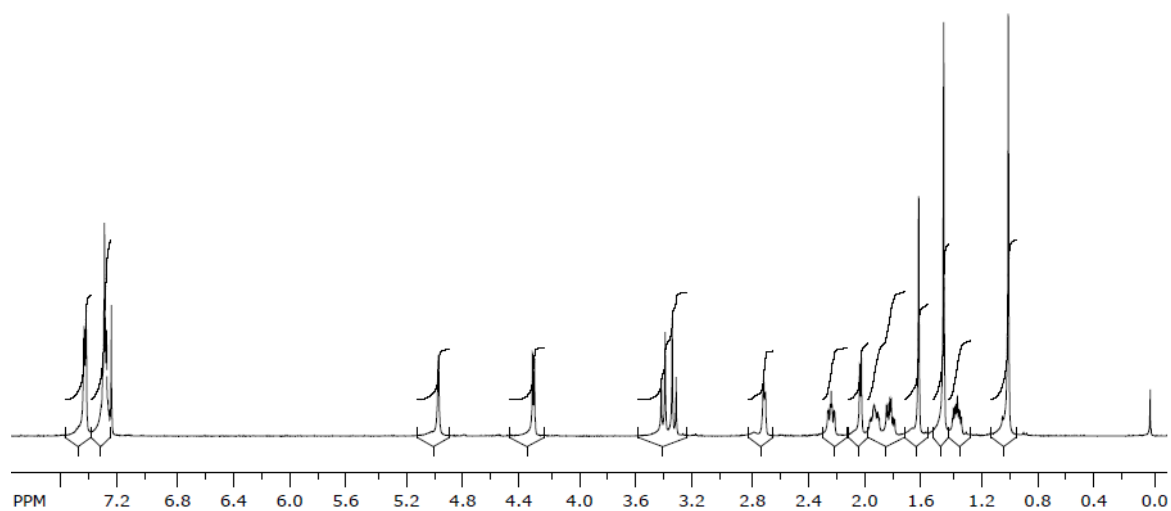
^{13}C NMR spectrum (125 MHz) of compound 17a



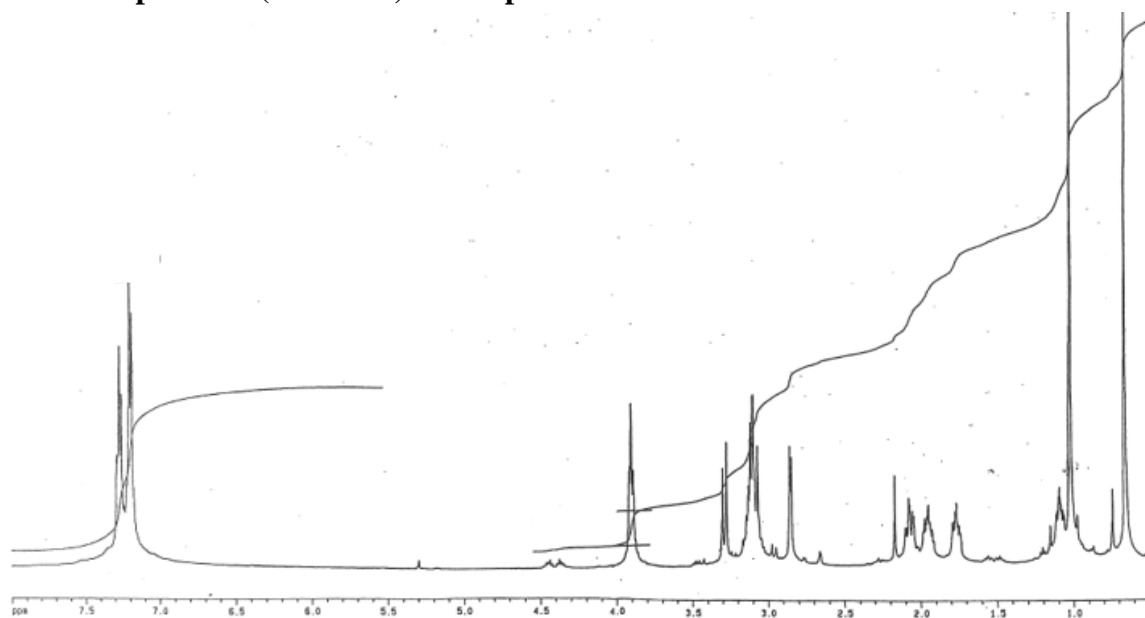
The ^1H NMR spectrum of 1,2-dichloroethane shows a triplet at approximately 3.7 ppm and a quartet at approximately 1.9 ppm. The x-axis represents the chemical shift in ppm, ranging from 0 to 5.0. The integration curve shows a step-like increase, indicating the relative areas under the peaks.

The ¹³C NMR spectrum of poly(2-vinylpyridine) displays several characteristic peaks. Aromatic carbons of the pyridine ring appear between 120 and 160 ppm, with a prominent peak at approximately 150 ppm. The backbone carbons, including the quaternary carbon of the pyridine ring and the methine carbons, are found in the 40-60 ppm range. A sharp peak at approximately 10 ppm corresponds to the methyl carbons of the pyridine ring. The spectrum shows a complex pattern of peaks due to the heterocyclic nature of the polymer.

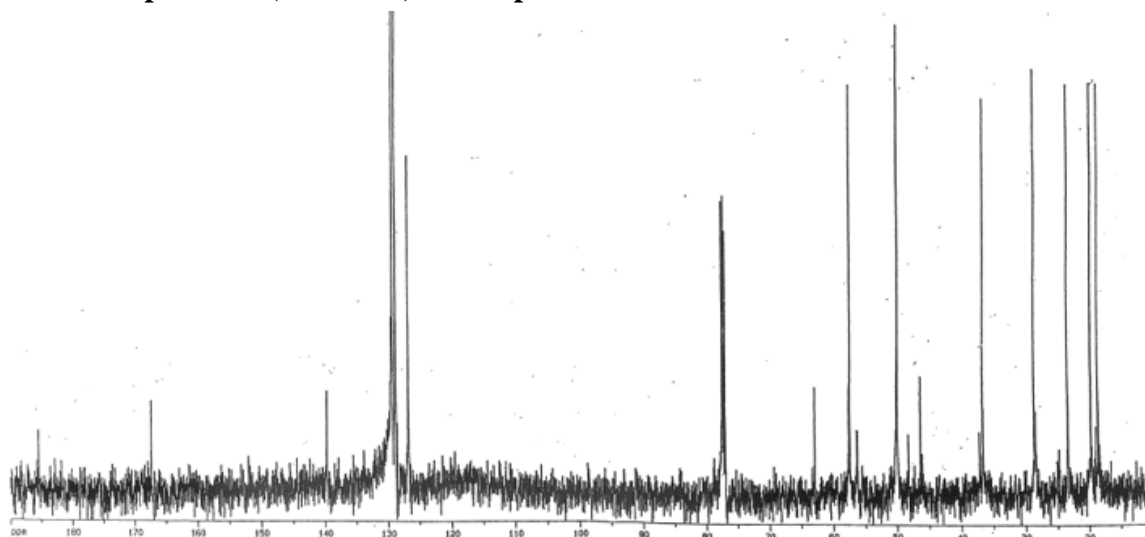
^1H NMR spectrum (500 MHz) of compound 18



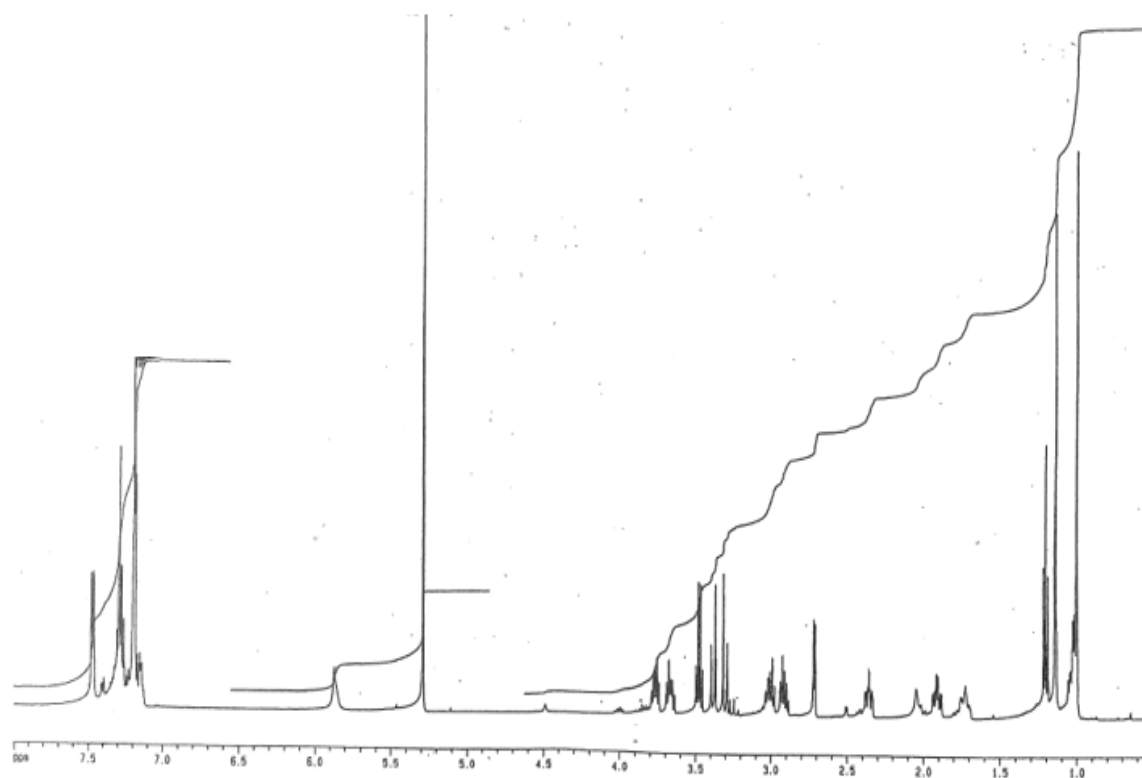
^1H NMR spectrum (500 MHz) of compound 19



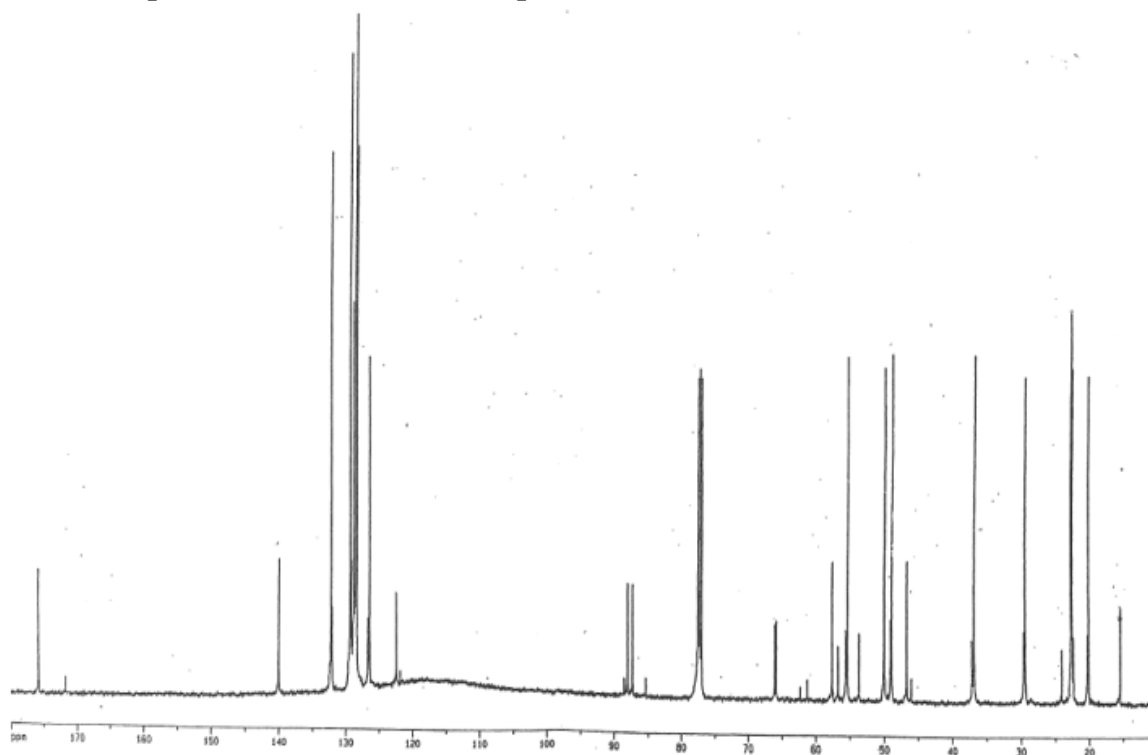
^{13}C NMR spectrum (125 MHz) of compound 19



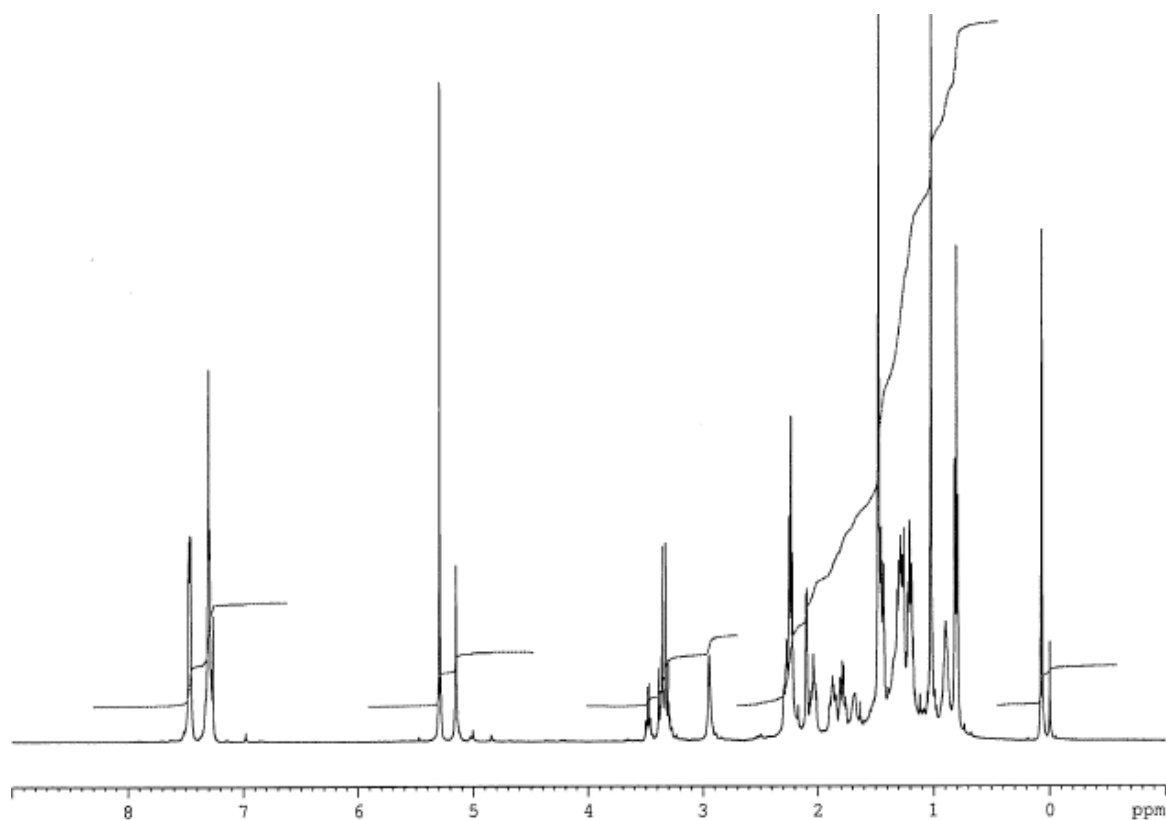
^1H NMR spectrum (500 MHz) of compound 20



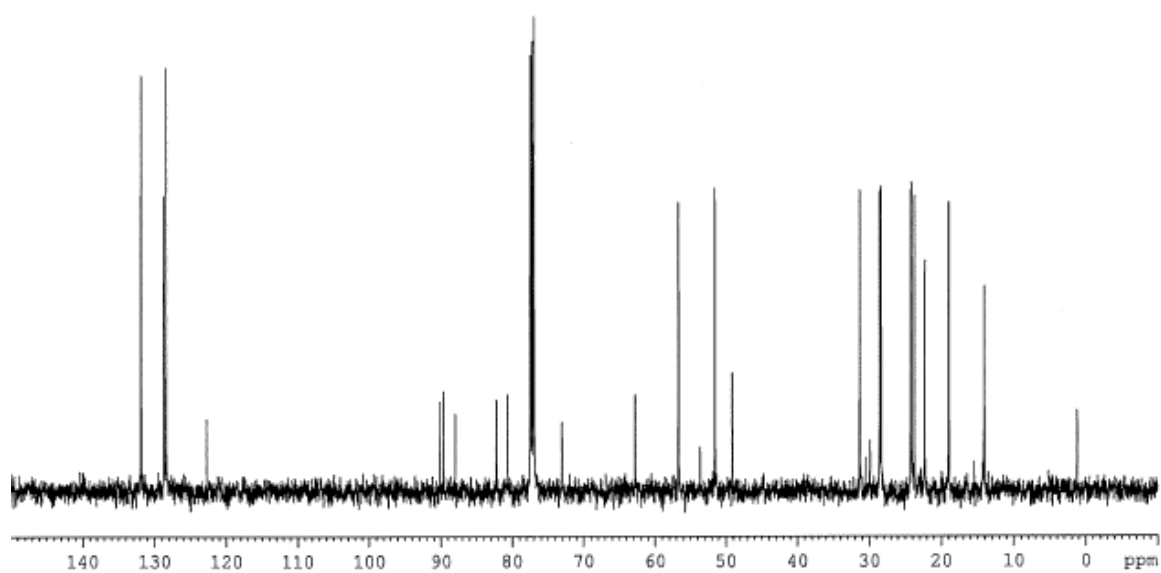
^{13}C NMR spectrum (125 MHz) of compound 20



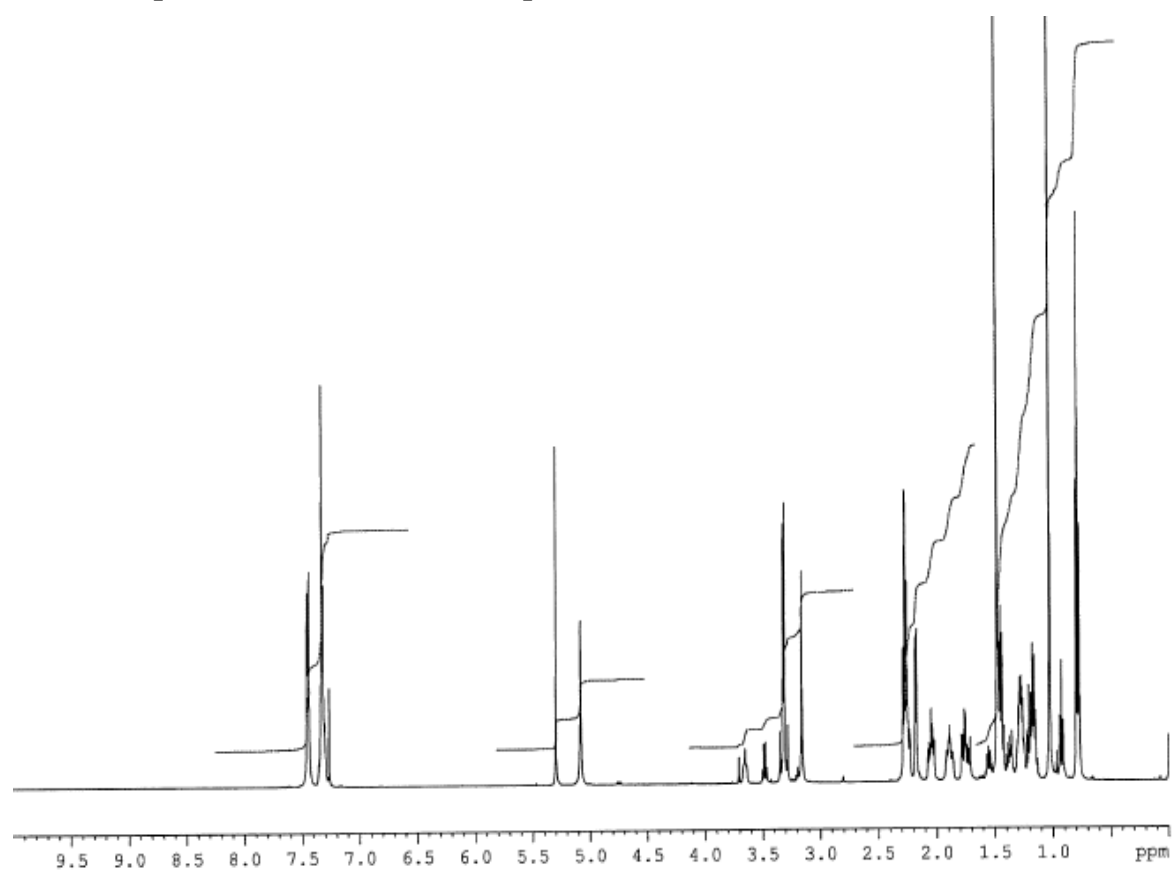
^1H NMR spectrum (500 MHz) of compound 21a



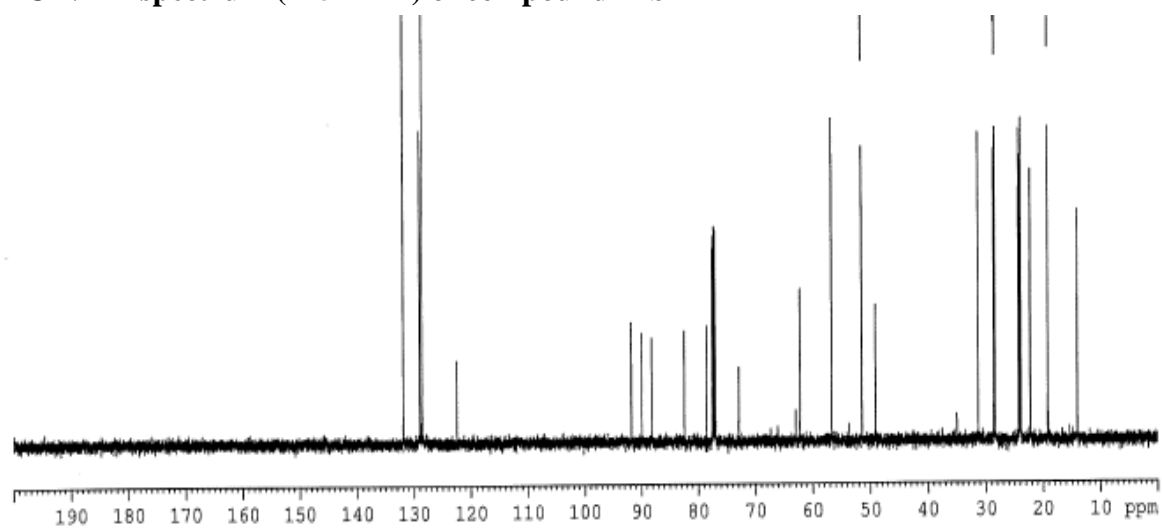
^{13}C NMR spectrum (125 MHz) of compound 21a



^1H NMR spectrum (500 MHz) of compound 21b

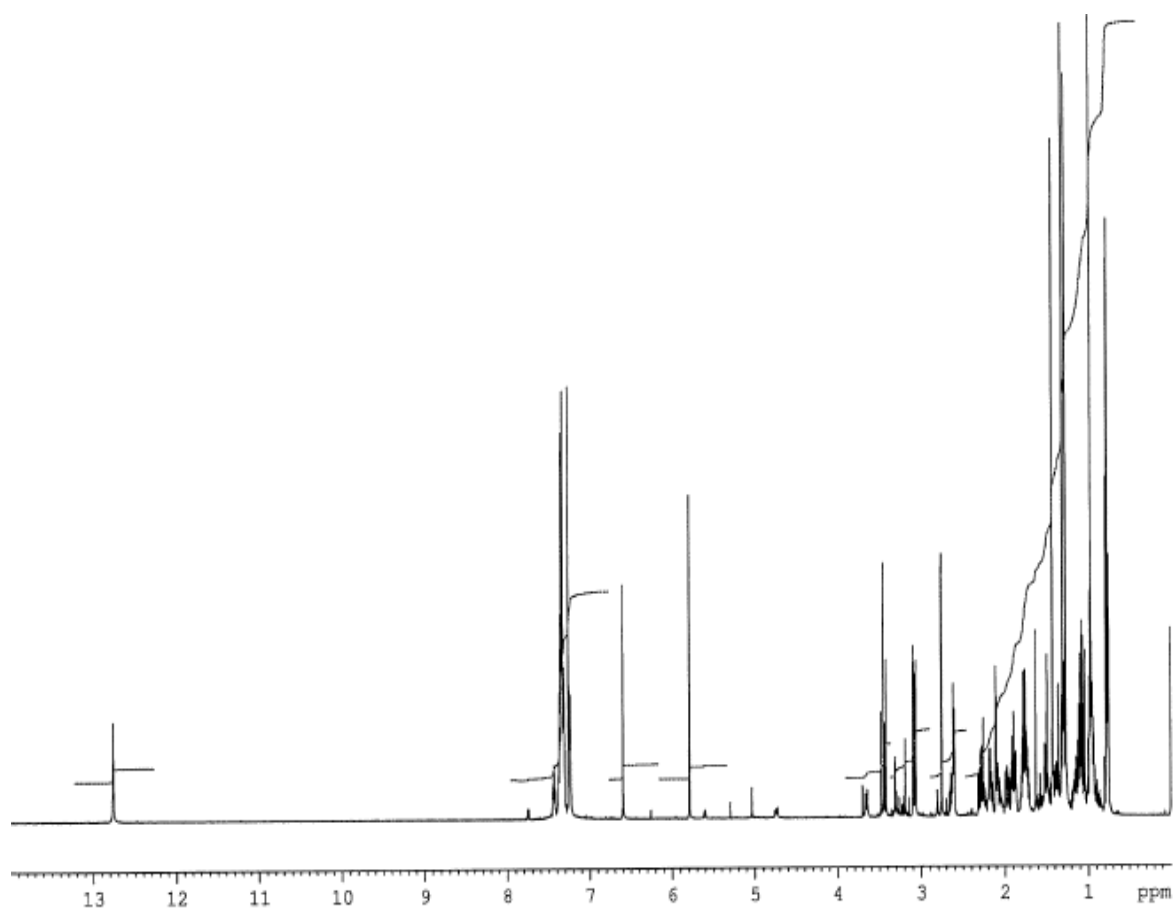


^{13}C NMR spectrum (125 MHz) of compound 21b

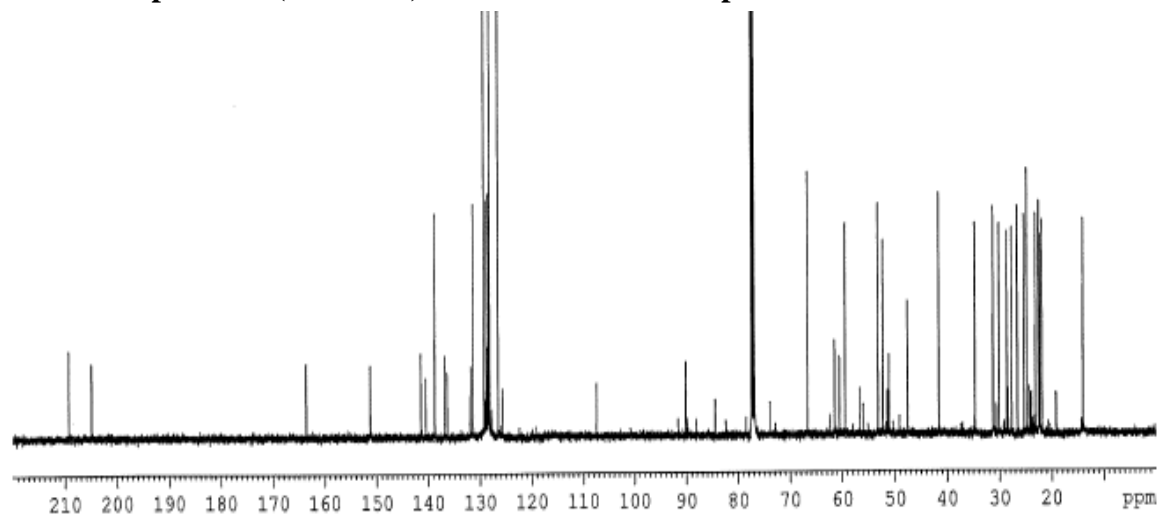


[illegible]

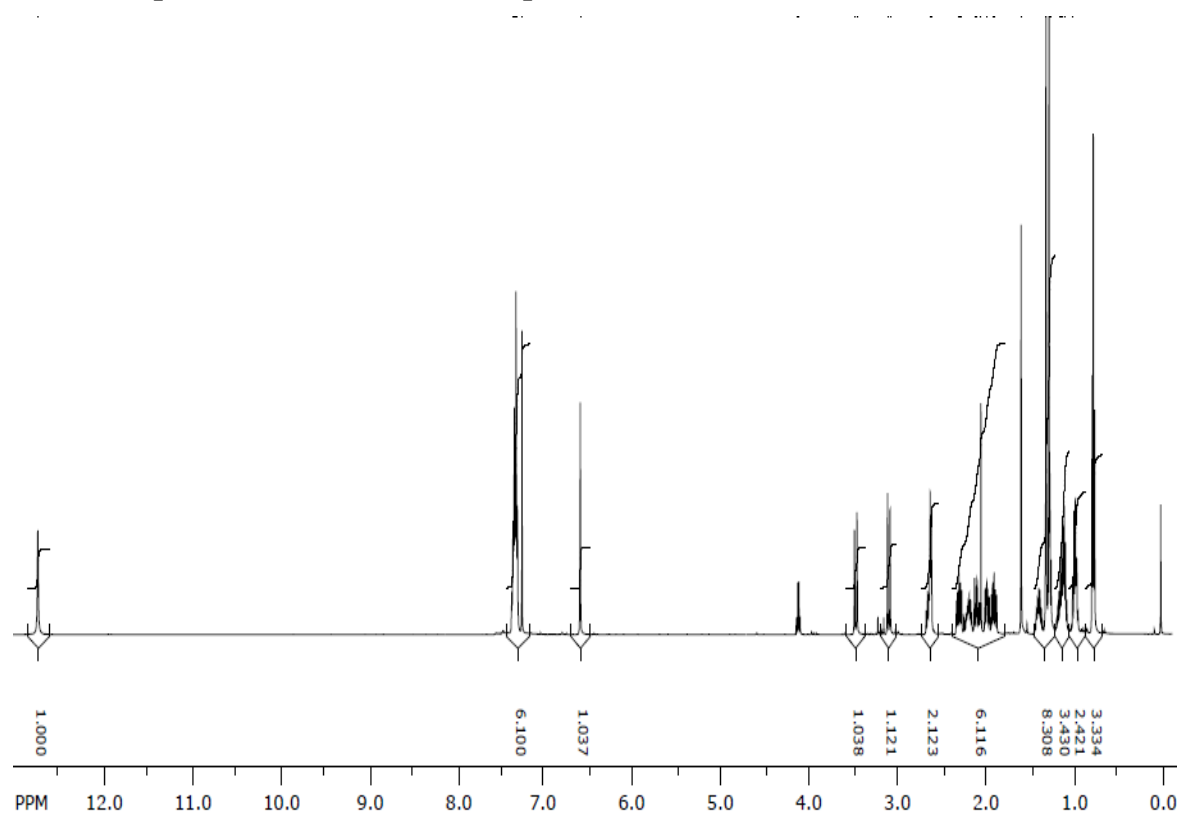
^1H NMR spectrum (500 MHz) of the crude reaction product 21b \rightarrow 22b + 23



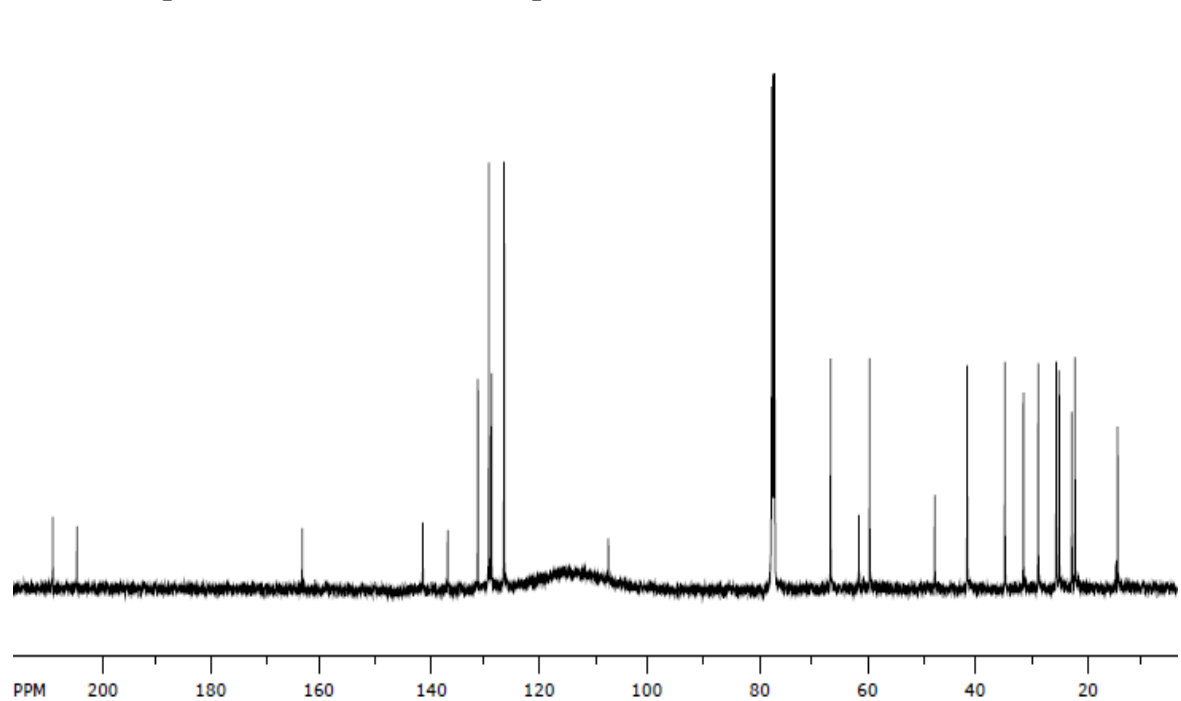
^{13}C NMR spectrum (125 MHz) of the crude reaction product 21b \rightarrow 22b + 23



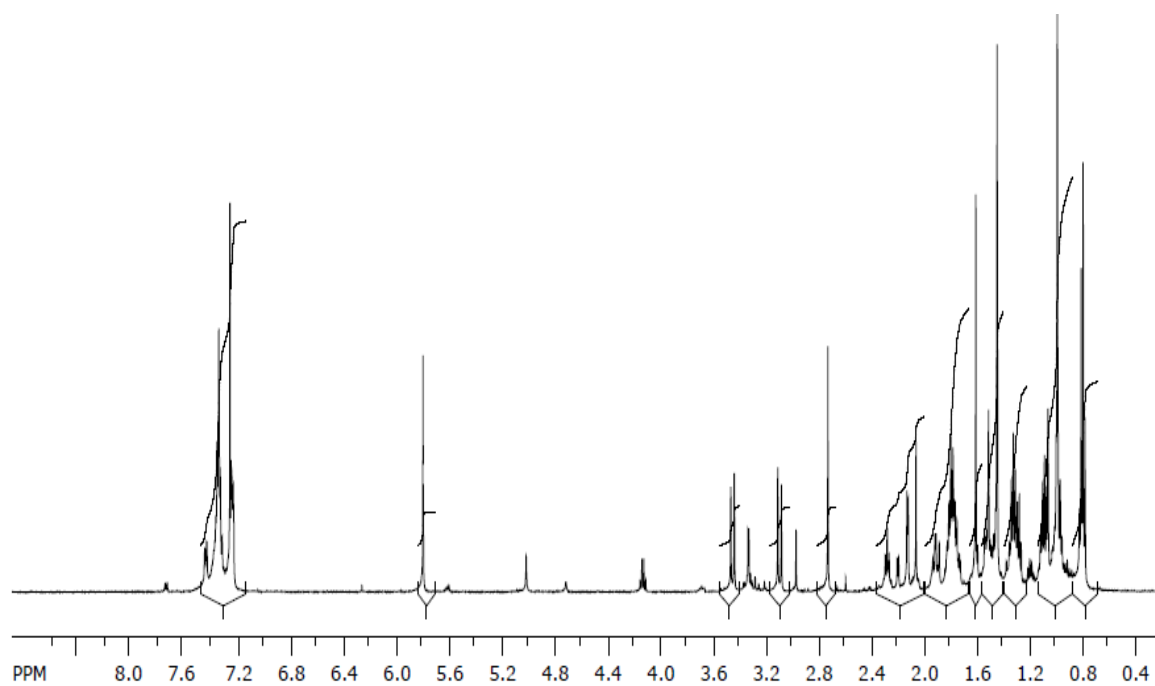
^1H NMR spectrum (500 MHz) of compound 22b



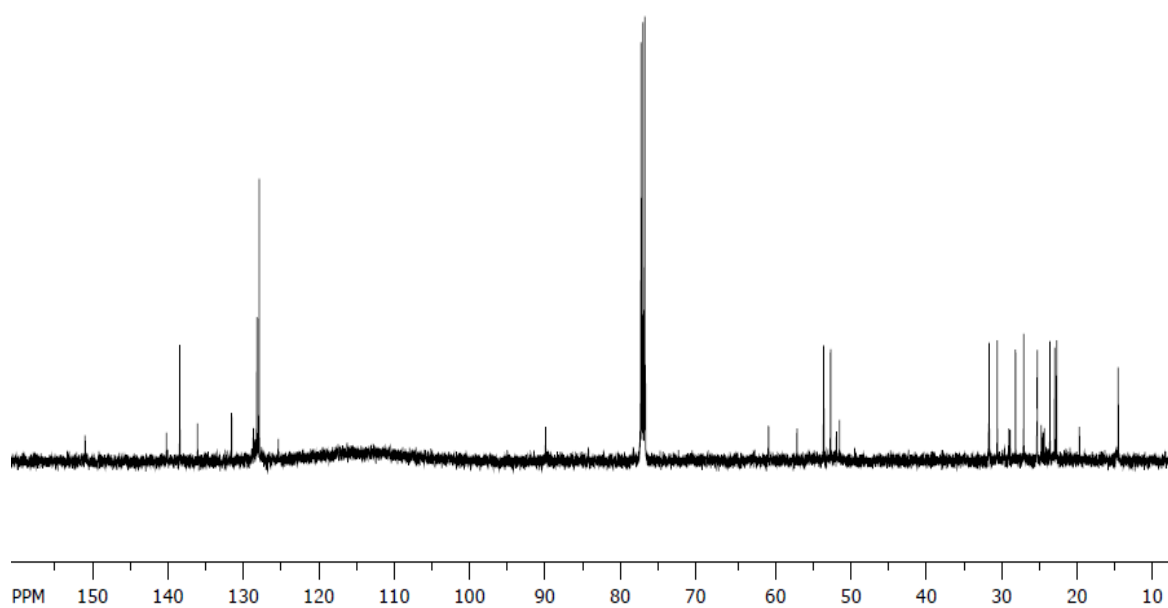
^{13}C NMR spectrum (125 MHz) of compound 22b



^1H NMR spectrum (500 MHz) of compound 23



^{13}C NMR spectrum (125 MHz) of compound 23



END of Supporting Material